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THIOBENZIMIDAZOLE DERIVATIVES

Abstract:

Thiobenzimidazole derivatives represented by general formula (1) or pharmaceutically acceptable sa

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Its thereof which have a potent human chymase inhibitory activity and, therefore, are usable as clinically applicable preventives and/or remedies for various diseases in which human chymase participates. <CHEM>

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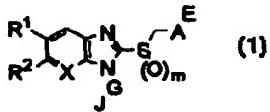
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(54) THIOBENZIMIDAZOLE DERIVATIVES

(57) Thiobenzimidazole derivatives represented by general formula (1) or pharmaceutically acceptable salts thereof which have a potent human chymase inhibitory activity and, therefore, are usable as clinically applicable preventives and/or remedies for various diseases in which human chymase participates.



Description**Technical Field**

5 [0001] The present invention relates to thiobenzimidazole derivatives represented by the formula (1) and, more specifically, thiobenzimidazole derivatives useful as inhibitors of human chymase activity.

Background Art

10 [0002] Chymase is one of the neutral proteases present in mast cell granules, and is deeply involved in a variety of biological processes in which mast cells participate. Various effects have been reported including, for example, the promotion of degranulation from mast cells, the activation of interleukin-1 β (IL-1 β), the activation of matrix protease, the decomposition of fibronectin and type IV collagen, the promotion of the release of transforming growth factor- β (TGF- β), the activation of substance P and vasoactive intestinal polypeptide (VIP), the conversion of angiotensin I (Ang I) to

15 Ang II, the conversion of endothelin, and the like.

[0003] The above indicates that inhibitors of said chymase activity may be promising as preventive and/or therapeutic agents for diseases of respiratory organs such as bronchial asthma, inflammatory/allergic diseases, for example allergic rhinitis, atopic dermatitis, and urticaria; diseases of circulatory organs, for example sclerosing vascular lesions, intravascular stenosis, disturbances of peripheral circulation, renal failure, and cardiac failure; diseases of bone/cartilage metabolism such as rheumatoid arthritis and osteoarthritis, and the like.

[0004] As inhibitors of chymase activity, there are known triazine derivatives (Japanese Unexamined Patent Publication (Kokai) No. 8-208654); hydantoin derivatives (Japanese Unexamined Patent Publication (Kokai) No. 9-31061); imidazolidine derivatives (PCT Application WO 96/04248); quinazoline derivatives (PCT Application WO 97/11941); heterocyclic amide derivatives (PCT Application WO 96/33974); and the like. However, the structures of these compounds are entirely different from those of the compounds of the present invention.

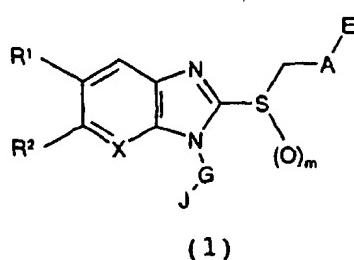
[0005] On the other hand, an art related to the compounds of the present invention is disclosed in U.S. Pat. No. 5,124,336. Said specification describes thiobenzimidazole derivatives as having an activity of antagonizing thromboxane receptor. The specification, however, makes no mention of the activity of said compounds to inhibit human chymase.

30 [0006] Thus, it is an object of the present invention to provide novel compounds that are potential and clinically applicable inhibitors of human chymase.

Disclosure of the Invention

35 [0007] Thus, after intensive research to attain the above objective, the applicants of the present invention have found the following 1 to 15 and have thereby completed the present invention.

1. A thiobenzimidazole derivative represented by the following formula (1):



50

wherein,

R¹ and R², simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R² together form -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-O-, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;

55 A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted

heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;

E represents COOR³, SO₃R³, CONHR³, SO₂NHR³, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R³ represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;

G represents a substituted or unsubstituted, linear or branched alkylene group having 1-6 carbons that may be interrupted with one or a plurality of O, S, SO₂, and NR³, in which R³ is as defined above and the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group; m represents an integer of 0 to 2;

when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring;

when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring; or

when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons,

a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a COOR³ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group; and

X represents CH or a nitrogen atom; or a medically acceptable salt thereof (hereinafter referred to as "the thiobenzimidazole derivative of the present invention").

2. The thiobenzimidazole derivative characterized in that, in the above formula (1), A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

3. The thiobenzimidazole derivative characterized in that, in the above formula (1), A is a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

4. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 1, or a medically acceptable salt thereof.

5. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 2, or a medically acceptable salt thereof.

6. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, and J is a substituted or unsubstituted aryl

group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

5 7. The thiobenzimidazole derivative characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, and J is a substituted or unsubstituted aryl group having 6 to 11 carbons or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

10 8. The thiobenzimidazole derivative characterized in that, in the above formula (1), G is -CH₂-, -CH₂CH₂-, -CH₂CO-, -CH₂CH₂O-, -CH₂CONH-, -CO-, -SO₂-, -CH₂SO₂-, -CH₂S- or -CH₂CH₂S-, or a medically acceptable salt thereof.

15 9. The thiobenzimidazole derivative characterized in that, in the above formula (1), R¹ and R² simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R², independently of each other, represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, a trihalomethyl group, a cyano group, or a hydroxy group, or a medically acceptable salt thereof.

20 10. The thiobenzimidazole derivative characterized in that, in the above formula (1), E represents COOH or a tetrazole group, or a medically acceptable salt thereof.

25 11. The thiobenzimidazole derivative characterized in that, in the above formula (1), X represents CH, or a medically acceptable salt thereof.

12. A thiobenzimidazole derivative characterized by having an activity of inhibiting human chymase, or a medically acceptable salt thereof.

25 13. A pharmaceutical composition comprising an at least one thiobenzimidazole derivative or a medically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition which is a preventive and/or therapeutic agent for a disease.

15. A preventive and/or therapeutic agent wherein said disease is an inflammatory disease, an allergic disease, a disease of respiratory organs, a disease of circulatory organs, or a disease of bone/cartilage metabolism.

30 Best Mode for Carrying Out the Invention

[0008] The present invention will now be explained in more detail below.

[0009] The above definitions concerning the substituents of the compounds of formula (1) of the present invention are as follows:

35 [0010] R¹ and R², simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R² together form -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-O-, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons. As the alkyl group having 1 to 4 carbons, there can be mentioned a methyl group, an ethyl group, a (n, i-) propyl group and a (n, i, s, t-) butyl group, and preferably a methyl group may be mentioned. Preferably R¹ and R² simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R², independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons, or an alkoxy group having 1 to 4 carbons. As the halogen atom, as used herein, there can be mentioned a fluorine atom, a chlorine atom, a bromine atom and the like, and preferably a chlorine atom and a fluorine atom

40 45 may be mentioned. As the alkyl group having 1 to 4 carbons, there can be mentioned a methyl group, an ethyl group, a (n, i-) propyl group and a (n, i, t-) butyl group, and preferably a methyl group may be mentioned. As the alkoxy group having 1 to 4 carbons, there can be mentioned a methoxy group, an ethoxy group, a (n, i-) propyloxy group and a (n, i, s, t-) butyloxy group, and preferably a methoxy group may be mentioned.

50 [0011] A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring. Preferably, there can be mentioned a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring. As the substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, there can be mentioned a methylene group, an ethylene group, a (n, i-) propylene group and a (n, i, t-) butylene group, and preferably an ethylene group may be mentioned. As the substituted or unsubstituted arylene group having 6 to 11 carbons, there can be mentioned a phenylene group, an indenylene group and a naphthylene group etc., and preferably a phenylene group

may be mentioned. As the substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, there can be mentioned a pyridilene group, a furanylene group, a thiophenylene group, an imidazolene group, a thiazolene group, a pyrimidilene group, an oxazolene group, an isoxazolene group, a benzphenylene group, a benzimidazolene group, a quinolinilene group, an indolene group, a benzothiazolene group and the like, and preferably a pyridilene group, a furanylene group, and a thiophenylene group may be mentioned.

[0012] Furthermore, as the substituent, as used herein, there can be mentioned a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons in which the substituent may be joined to each other at adjacent sites via an acetal bond, a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, or a phenoxy group that may be substituted with one or more halogen atoms. They may be independently substituted at any one or more sites of the ring or the alkylene group. Specifically, there can be mentioned OH, a chloro group, a bromo group, a nitro group, a methoxy group, a cyano group, a methylenedioxy group, a trifluoromethyl group, a methyl group, an ethyl group, a (n, i-) propyl group, a (n, i, t-) butyl group, and the like.

[0013] As E, there can be mentioned COOR³, SO₃R³, CONHR³, SO₂NHR³, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group, and preferably COOR³ or a tetrazole group may be mentioned. As R³ as used herein, there can be mentioned a hydrogen atom or a linear or branched alkyl group having 1 to 6 carbons, and preferably a hydrogen atom, a methyl group, an ethyl group, or a t-butyl group may be mentioned, and most preferably a hydrogen atom may be mentioned.

[0014] G represents a substituted or unsubstituted, linear or branched alkyl group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO₂, and NR³, in which R³ is as defined above and the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group. Specifically, there can be mentioned -CH₂- , -CH₂CH₂- , -CH₂CO-, -CH₂CH₂O-, CH₂CONH-, -CO-, -SO₂-, -CH₂SO₂-, -CH₂S-, -CH₂CH₂S- and the like, and preferably -CH₂- , -CH₂CH₂- , -CH₂CO- or -CH₂CH₂O- may be mentioned.

[0015] m represents an integer of 0 to 2, and preferably 0 or 2 may be mentioned.

[0016] When m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring. Preferably, a substituted aryl group having 10 to 11 carbons and a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring may be mentioned. As the substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, there can be mentioned a methyl group, an ethyl group, a (n, i-) propyl group, a (n, i, s, t-) butyl group, a (n, i, ne, t-) pentyl group and a cyclohexyl group. As the substituted or unsubstituted aryl group having 7 to 9 carbons, there can be mentioned an indenyl group, and as the substituted aryl group having 10 to 11 carbons, there can be mentioned a naphthyl group. As the substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, there can be mentioned a pyridyl group, a furanyl group, a thiophenyl group, an imidazole group, a thiazole group, a pyrimidine group, an oxazole group, an isoxazole group, a benzofuran group, a benzimidazole group, a quinoline group, an isoquinoline group, a quinoxaline group, a benzoxadiazole group, a benzothiadiazole group, an indole group, a N-methylindole group, a benzothiazole group, a benzothiophenyl group, a benzisoxazole group and the like, and preferably a benzothiophenyl group or a N-methylindole group may be mentioned.

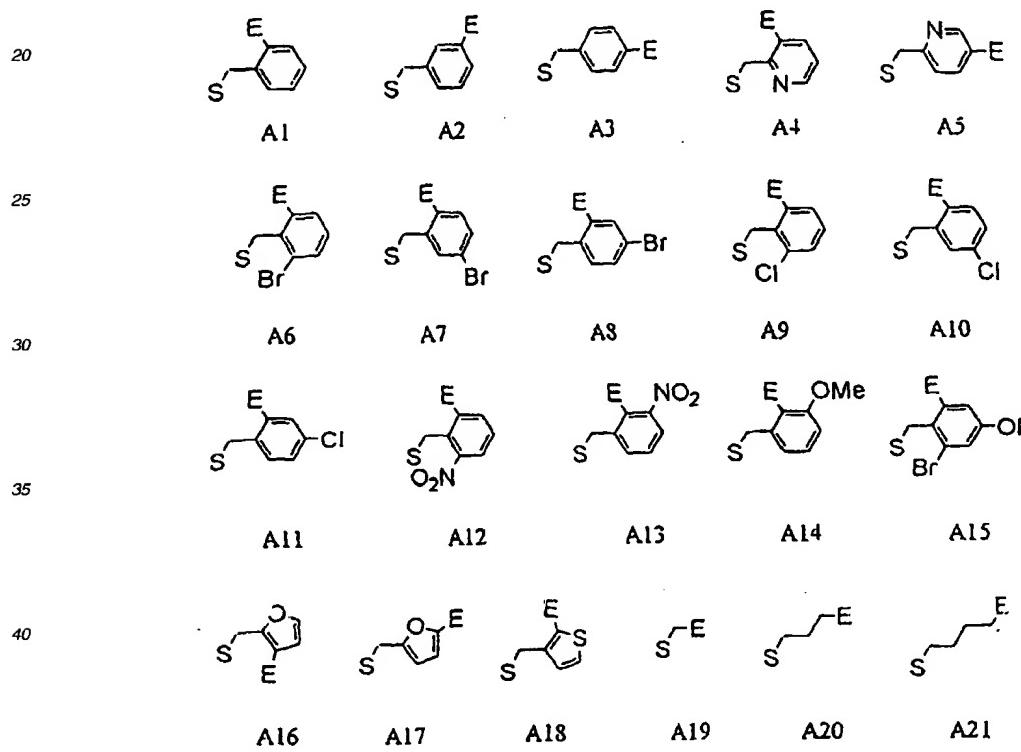
[0017] When m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, and preferably a substituted or unsubstituted aryl group having 6 to 11 carbons and a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring may be mentioned. As the substituted or unsubstituted aryl group having 6 to 11 carbons, there can be mentioned a phenyl group, an indenyl group, a naphthyl group and the like, and preferably a phenyl group or a naphthyl group may be mentioned. As the substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons and as the substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, there can be mentioned those described above. As the substituent as used herein, there can be mentioned, a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons,

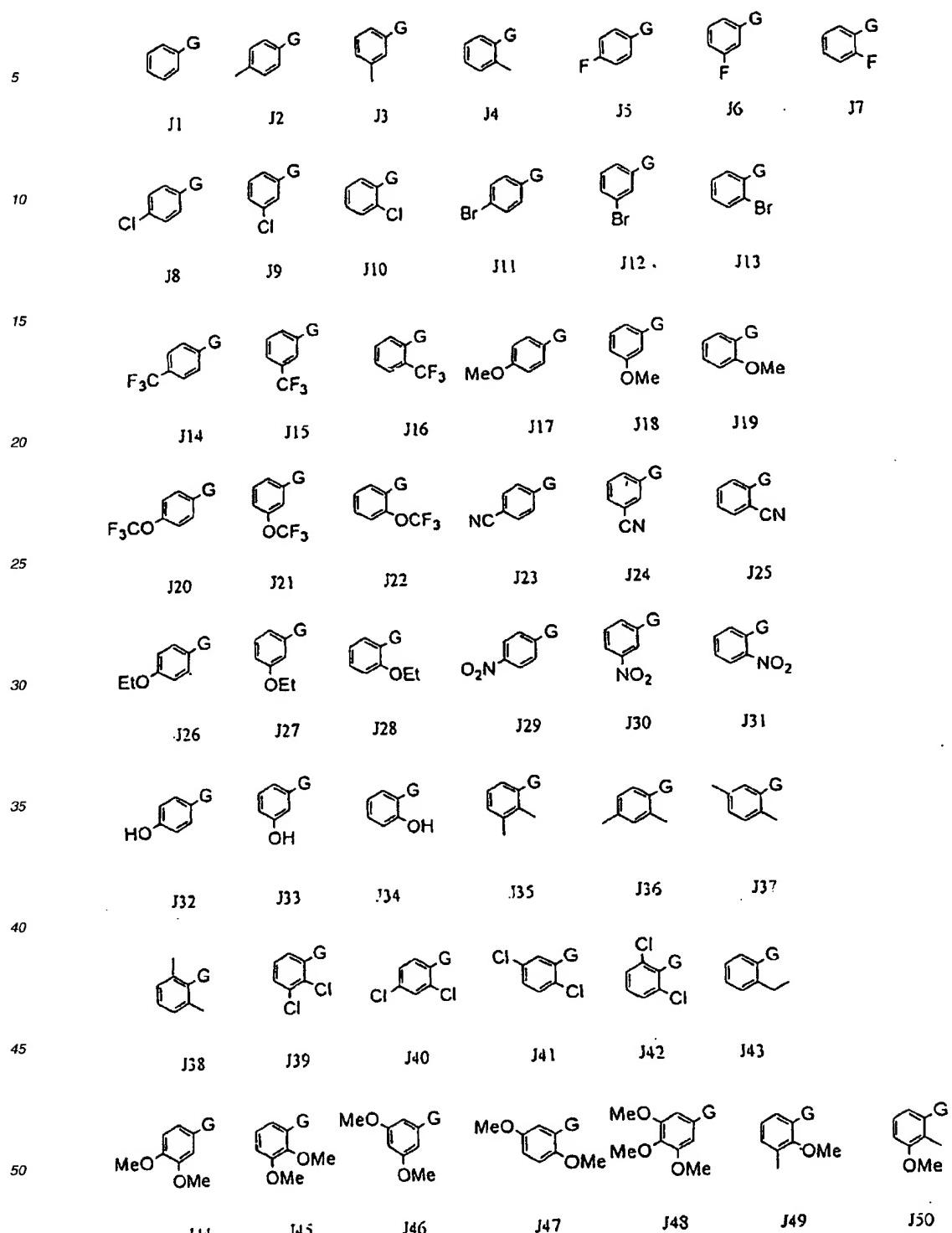
a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, or a phenoxy group that may be substituted with one or more halogen atoms. They may be independently substituted at any one or more sites of the ring or the alkyl group. Specifically, there can be mentioned OH, a chloro group, a bromo group, a nitro group, a methoxy group, a cyano group, a methylenedioxy group, a trifluoromethyl group, a trifluoromethoxy group, a methyl group, an ethyl group, a (n, i-) propyl group, a (n, i, s, t-) butyl group, an anilide group and the like.

10 [0018] X represents CH or a nitrogen atom, and preferably CH may be mentioned.

[0019] As the compound of formula (1), specifically those described in Tables 1 to 40 are preferred. Most preferred among them are compounds Nos. 37, 50, 63, 64, 65, 84, 115, 117, 119, 121, 123, 130, 143, 147, 168, 174, 256, 264, 272, 311, 319, 320, 321, 324, 349, 352, 354, 355, 358, 364, 380, 392, 395, 398, 401, 402, 444, 455, 459, 460, 506, 863, 866, and 869.

15 [0020] A1 to A21 and J1 to J85 described in Tables 1 to 40 are the groups shown below, in which E and G are as described above.





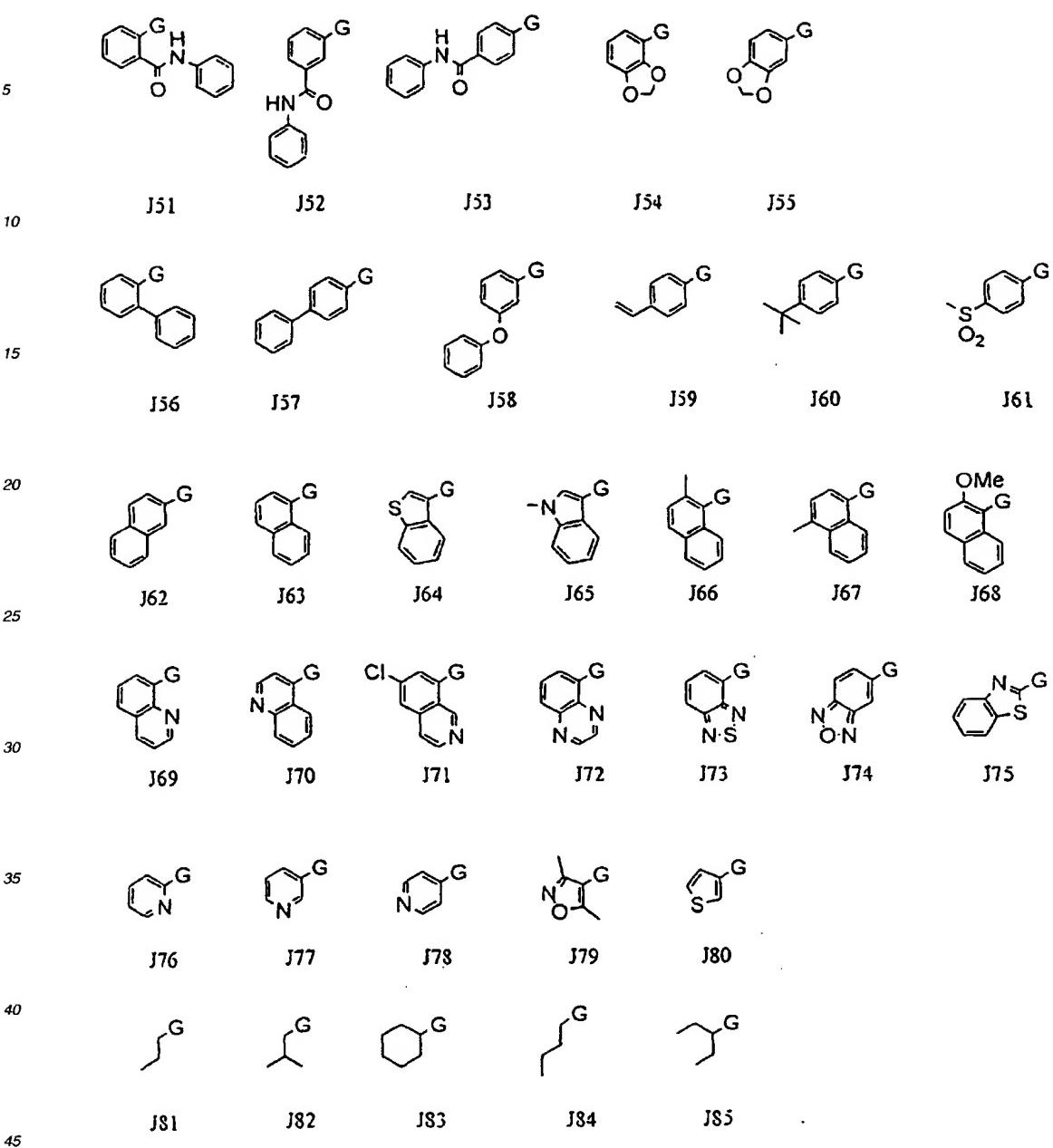


Table 1

Compound No.	R ¹	R ²	A	E	G	J	m	X
1	H	H	A1	COOH	CH ₂ CH ₂	J1	0	CH
2	H	H	A1	COOH	CH ₂	J2	0	CH
3	H	H	A1	COOH	CH ₂	J3	0	CH
4	H	H	A1	COOH	CH ₂	J4	0	CH

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Table 1 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X	
5	H	H	A1	COOH	CH ₂	J5	0	CH	
6	H	H	A1	COOH	CH ₂	J6	0	CH	
7	H	H	A1	COOH	CH ₂	J7	0	CH	
8	H	H	A1	COOH	CH ₂	J8	0	CH	
9	H	H	A1	COOH	CH ₂	J9	0	CH	
10	10	H	H	A1	COOH	CH ₂	J10	0	CH
11	H	H	A1	COOH	CH ₂	J11	0	CH	
12	H	H	A1	COOH	CH ₂	J12	0	CH	
15	13	H	H	A1	COOH	CH ₂	J13	0	CH
14	H	H	A1	COOH	CH ₂	J14	0	CH	
15	15	H	H	A1	COOH	CH ₂	J15	0	CH
20	16	H	H	A1	COOH	CH ₂	J16	0	CH
17	H	H	A1	COOH	CH ₂	J17	0	CH	
18	H	H	A1	COOH	CH ₂	J18	0	CH	
19	H	H	A1	COOH	CH ₂	J19	0	CH	
25	20	H	H	A1	COOH	CH ₂	J20	0	CH
21	H	H	A1	COOH	CH ₂	J21	0	CH	
22	H	H	A1	COOH	CH ₂	J22	0	CH	
30	23	H	H	A1	COOH	CH ₂	J23	0	CH
24	H	H	A1	COOH	CH ₂	J24	0	CH	
35	25	H	H	A1	COOH	CH ₂	J25	0	CH

35

Table 2

Compound No.	R ¹	R ²	A	E	G	J	m	X	
40	26	H	H	A1	COOH	CH ₂	J26	0	CH
27	H	H	A1	COOH	CH ₂	J27	0	CH	
45	28	H	H	A1	COOH	CH ₂	J28	0	CH
29	H	H	A1	COOH	CH ₂	J29	0	CH	
50	30	H	H	A1	COOH	CH ₂	J30	0	CH
31	H	H	A1	COOH	CH ₂	J31	0	CH	
32	H	H	A1	COOH	CH ₂	J32	0	CH	
55	33	H	H	A1	COOH	CH ₂	J33	0	CH
34	H	H	A1	COOH	CH ₂	J34	0	CH	
35	H	H	A1	COOH	CH ₂	J35	0	CH	
36	H	H	A1	COOH	CH ₂	J36	0	CH	
37	H	H	A1	COOH	CH ₂	J37	0	CH	
38	H	H	A1	COOH	CH ₂	J38	0	CH	

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Table 2 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
39	H	H	A1	COOH	CH ₂	J39	0	CH
40	H	H	A1	COOH	CH ₂	J40	0	CH
41	H	H	A1	COOH	CH ₂	J41	0	CH
42	H	H	A1	COOH	CH ₂	J42	0	CH
43	H	H	A1	COOH	CH ₂	J43	0	CH
44	H	H	A1	COOH	CH ₂	J44	0	CH
45	H	H	A1	COOH	CH ₂	J45	0	CH
46	H	H	A1	COOH	CH ₂	J46	0	CH
47	H	H	A1	COOH	CH ₂	J47	0	CH
48	H	H	A1	COOH	CH ₂	J48	0	CH
49	H	H	A1	COOH	CH ₂	J49	0	CH
50	H	H	A1	COOH	CH ₂	J50	0	CH

Table 3

Compound No.	R ¹	R ²	A	E	G	J	m	X
51	H	H	A1	COOH	CH ₂	J51	0	CH
52	H	H	A1	COOH	CH ₂	J52	0	CH
53	H	H	A1	COOH	CH ₂	J53	0	CH
54	H	H	A1	COOH	CH ₂	J54	0	CH
55	H	H	A1	COOH	CH ₂	J55	0	CH
56	H	H	A1	COOH	CH ₂	J56	0	CH
57	H	H	A1	COOH	CH ₂	J57	0	CH
58	H	H	A1	COOH	CH ₂	J58	0	CH
59	H	H	A1	COOH	CH ₂	J59	0	CH
60	H	H	A1	COOH	CH ₂	J60	0	CH
61	H	H	A1	COOH	CH ₂	J61	0	CH
62	H	H	A1	COOH	CH ₂	J62	0	CH
63	H	H	A1	COOH	CH ₂	J63	0	CH
64	H	H	A1	COOH	CH ₂	J64	0	CH
65	H	H	A1	COOH	CH ₂	J65	0	CH
66	H	H	A1	COOH	CH ₂	J66	0	CH
67	H	H	A1	COOH	CH ₂	J67	0	CH
68	H	H	A1	COOH	CH ₂	J68	0	CH
69	H	H	A1	COOH	CH ₂	J69	0	CH
70	H	H	A1	COOH	CH ₂	J70	0	CH
71	H	H	A1	COOH	CH ₂	J71	0	CH
72	H	H	A1	COOH	CH ₂	J72	0	CH

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Table 3 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
73	H	H	A1	COOH	CH ₂	J73	0	CH
74	H	H	A1	COOH	CH ₂	J74	0	CH
75	H	H	A1	COOH	CH ₂	J75	0	CH

10

Table 4

Compound No.	R ¹	R ²	A	E	G	J	m	X
76	H	H	A1	COOH	CH ₂	J76	0	CH
77	H	H	A1	COOH	CH ₂	J77	0	CH
78	H	H	A1	COOH	CH ₂	J78	0	CH
79	H	H	A1	COOH	CH ₂	J79	0	CH
80	H	H	A1	COOH	CH ₂	J80	0	CH
81	Me	Me	A1	COOH	CH ₂	J1	0	CH
82	Me	Me	A1	COOH	CH ₂	J2	0	CH
83	Me	Me	A1	COOH	CH ₂	J3	0	CH
84	Me	Me	A1	COOH	CH ₂	J4	0	CH
85	Me	Me	A1	COOH	CH ₂	J5	0	CH
86	Me	Me	A1	COOH	CH ₂	J6	0	CH
87	Me	Me	A1	COOH	CH ₂	J7	0	CH
88	Me	Me	A1	COOH	CH ₂	J8	0	CH
89	Me	Me	A1	COOH	CH ₂	J9	0	CH
90	Me	Me	A1	COOH	CH ₂	J10	0	CH
91	Me	Me	A1	COOH	CH ₂	J11	0	CH
92	Me	Me	A1	COOH	CH ₂	J12	0	CH
93	Me	Me	A1	COOH	CH ₂	J13	0	CH
94	Me	Me	A1	COOH	CH ₂	J14	0	CH
95	Me	Me	A1	COOH	CH ₂	J15	0	CH
96	Me	Me	A1	COOH	CH ₂	J16	0	CH
97	Me	Me	A1	COOH	CH ₂	J17	0	CH
98	Me	Me	A1	COOH	CH ₂	J18	0	CH
99	Me	Me	A1	COOH	CH ₂	J19	0	CH
100	Me	Me	A1	COOH	CH ₂	J20	0	CH

50

Table 5

Compound No.	R ¹	R ²	A	E	G	J	m	X
101	Me	Me	A1	COOH	CH ₂	J21	0	CH

55

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Table 5 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	102	Me	Me	A1	COOH	CH ₂	J22	0	CH
	103	Me	Me	A1	COOH	CH ₂	J23	0	CH
	104	Me	Me	A1	COOH	CH ₂	J24	0	CH
	105	Me	Me	A1	COOH	CH ₂	J25	0	CH
	106	Me	Me	A1	COOH	CH ₂	J26	0	CH
10	107	Me	Me	A1	COOH	CH ₂	J27	0	CH
	108	Me	Me	A1	COOH	CH ₂	J28	0	CH
	109	Me	Me	A1	COOH	CH ₂	J29	0	CH
	110	Me	Me	A1	COOH	CH ₂	J30	0	CH
	111	Me	Me	A1	COOH	CH ₂	J31	0	CH
15	112	Me	Me	A1	COOH	CH ₂	J32	0	CH
	113	Me	Me	A1	COOH	CH ₂	J33	0	CH
	114	Me	Me	A1	COOH	CH ₂	J34	0	CH
	115	Me	Me	A1	COOH	CH ₂	J35	0	CH
	116	Me	Me	A1	COOH	CH ₂	J36	0	CH
20	117	Me	Me	A1	COOH	CH ₂	J37	0	CH
	118	Me	Me	A1	COOH	CH ₂	J38	0	CH
	119	Me	Me	A1	COOH	CH ₂	J39	0	CH
	120	Me	Me	A1	COOH	CH ₂	J40	0	CH
	121	Me	Me	A1	COOH	CH ₂	J41	0	CH
25	122	Me	Me	A1	COOH	CH ₂	J42	0	CH
	123	Me	Me	A1	COOH	CH ₂	J43	0	CH
	124	Me	Me	A1	COOH	CH ₂	J44	0	CH
	125	Me	Me	A1	COOH	CH ₂	J45	0	CH

40

Table 6

	Compound No.	R ¹	R ²	A	E	G	J	m	X
45	126	Me	Me	A1	COOH	CH ₂	J46	0	CH
	127	Me	Me	A1	COOH	CH ₂	J47	0	CH
	128	Me	Me	A1	COOH	CH ₂	J48	0	CH
	129	Me	Me	A1	COOH	CH ₂	J49	0	CH
	130	Me	Me	A1	COOH	CH ₂	J50	0	CH
50	131	Me	Me	A1	COOH	CH ₂	J51	0	CH
	132	Me	Me	A1	COOH	CH ₂	J52	0	CH
	133	Me	Me	A1	COOH	CH ₂	J53	0	CH
	134	Me	Me	A1	COOH	CH ₂	J54	0	CH
55									

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Table 6 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	135	Me	Me	A1	COOH	CH ₂	J55	0	CH
	136	Me	Me	A1	COOH	CH ₂	J56	0	CH
	137	Me	Me	A1	COOH	CH ₂	J57	0	CH
	138	Me	Me	A1	COOH	CH ₂	J58	0	CH
10	139	Me	Me	A1	COOH	CH ₂	J59	0	CH
	140	Me	Me	A1	COOH	CH ₂	J60	0	CH
	141	Me	Me	A1	COOH	CH ₂	J61	0	CH
	142	Me	Me	A1	COOH	CH ₂	J62	0	CH
15	143	Me	Me	A1	COOH	CH ₂	J63	0	CH
	144	Me	Me	A1	COOH	CH ₂	J64	0	CH
	145	Me	Me	A1	COOH	CH ₂	J65	0	CH
	146	Me	Me	A1	COOH	CH ₂	J66	0	CH
20	147	Me	Me	A1	COOH	CH ₂	J67	0	CH
	148	Me	Me	A1	COOH	CH ₂	J68	0	CH
	149	Me	Me	A1	COOH	CH ₂	J69	0	CH
	150	Me	Me	A1	COOH	CH ₂	J70	0	CH

Table 7

	Compound No.	R ¹	R ²	A	E	G	J	m	X
35	151	Me	Me	A1	COOH	CH ₂	J71	0	CH
	152	Me	Me	A1	COOH	CH ₂	J72	0	CH
	153	Me	Me	A1	COOH	CH ₂	J73	0	CH
	154	Me	Me	A1	COOH	CH ₂	J74	0	CH
40	155	Me	Me	A1	COOH	CH ₂	J75	0	CH
	156	Me	Me	A1	COOH	CH ₂	J76	0	CH
	157	Me	Me	A1	COOH	CH ₂	J77	0	CH
	158	Me	Me	A1	COOH	CH ₂	J78	0	CH
45	159	Me	Me	A1	COOH	CH ₂	J79	0	CH
	160	Me	Me	A1	COOH	CH ₂	J80	0	CH
	161	Cl	Cl	A1	COOH	CH ₂ CH ₂	J1	0	CH
	162	Cl	Cl	A1	COOH	CH ₂	J4	0	CH
50	163	Cl	Cl	A1	COOH	CH ₂	J10	0	CH
	164	Cl	Cl	A1	COOH	CH ₂	J18	0	CH
	165	Cl	Cl	A1	COOH	CH ₂	J21	0	CH
	166	Cl	Cl	A1	COOH	CH ₂	J28	0	CH
55	167	Cl	Cl	A1	COOH	CH ₂	J35	0	CH

Table 7 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
168	Cl	Cl	A1	COOH	CH ₂	J37	0	CH
169	Cl	Cl	A1	COOH	CH ₂	J39	0	CH
170	Cl	Cl	A1	COOH	CH ₂	J43	0	CH
171	Cl	Cl	A1	COOH	CH ₂	J46	0	CH
172	Cl	Cl	A1	COOH	CH ₂	J50	0	CH
173	Cl	Cl	A1	COOH	CH ₂	J54	0	CH
174	Cl	Cl	A1	COOH	CH ₂	J63	0	CH
175	Cl	Cl	A1	COOH	CH ₂	J64	0	CH

15

Table 8

Compound No.	R ¹	R ²	A	E	G	J	m	X
176	Cl	Cl	A1	COOH	CH ₂	J65	0	CH
177	Cl	Cl	A1	COOH	CH ₂	J66	0	CH
178	Cl	Cl	A1	COOH	CH ₂	J67	0	CH
179	Cl	Cl	A1	COOH	CH ₂	J71	0	CH
180	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂ CH ₂	J1	0	CH	
181	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J4	0	CH	
182	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J10	0	CH	
183	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J18	0	CH	
184	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J21	0	CH	
185	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J28	0	CH	
186	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J35	0	CH	
187	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J37	0	CH	
188	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J39	0	CH	
189	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J43	0	CH	
190	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J46	0	CH	
191	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J50	0	CH	
192	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J54	0	CH	
193	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J63	0	CH	
194	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J64	0	CH	
195	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J65	0	CH	
196	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J66	0	CH	
197	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J67	0	CH	
198	-CH ₂ CH ₂ CH ₂ -	A1	COOH	CH ₂	J71	0	CH	
199	-OCH ₂ O-	A1	COOH	CH ₂ CH ₂	J1	0	CH	
200	-OCH ₂ O-	A1	COOH	CH ₂	J4	0	CH	

Table 9

Compound No.	R ¹	R ²	A	E	G	J	m	X
201	-OCH ₂ O-	A1	COOH	CH ₂	J10	0	CH	
202	-OCH ₂ O-	A1	COOH	CH ₂	J18	0	CH	
203	-OCH ₂ O-	A1	COOH	CH ₂	J21	0	CH	
204	-OCH ₂ O-	A1	COOH	CH ₂	J28	0	CH	
205	-OCH ₂ O-	A1	COOH	CH ₂	J35	0	CH	
206	-OCH ₂ O-	A1	COOH	CH ₂	J37	0	CH	
207	-OCH ₂ O-	A1	COOH	CH ₂	J39	0	CH	
208	-OCH ₂ O-	A1	COOH	CH ₂	J43	0	CH	
209	-OCH ₂ O-	A1	COOH	CH ₂	J46	0	CH	
210	-OCH ₂ O-	A1	COOH	CH ₂	J50	0	CH	
211	-OCH ₂ O-	A1	COOH	CH ₂	J54	0	CH	
212	-OCH ₂ O-	A1	COOH	CH ₂	J63	0	CH	
213	-OCH ₂ O-	A1	COOH	CH ₂	J64	0	CH	
214	-OCH ₂ O-	A1	COOH	CH ₂	J65	0	CH	
215	-OCH ₂ O-	A1	COOH	CH ₂	J66	0	CH	
216	-OCH ₂ O-	A1	COOH	CH ₂	J67	0	CH	
217	-OCH ₂ O-	A1	COOH	CH ₂	J71	0	CH	
218	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂ CH ₂	J1	0	CH	
219	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J4	0	CH	
220	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J10	0	CH	
221	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J18	0	CH	
222	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J35	0	CH	
223	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J37	0	CH	
224	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J39	0	CH	
225	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J50	0	CH	

Table 10

Compound No.	R ¹	R ²	A	E	G	J	m	X
226	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J63	0	CH	
227	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J64	0	CH	
228	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J65	0	CH	
229	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J67	0	CH	
230	-OCH ₂ CH ₂ O-	A1	COOH	CH ₂	J71	0	CH	
231	OMe	OMe	A1	COOH	CH ₂ CH ₂	J1	0	CH

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Table 10 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	232	OMe	OMe	A1	COOH	CH ₂	J4	0	CH
	233	OMe	OMe	A1	COOH	CH ₂	J10	0	CH
	234	OMe	OMe	A1	COOH	CH ₂	J18	0	CH
	235	OMe	OMe	A1	COOH	CH ₂	J35	0	CH
	236	OMe	OMe	A1	COOH	CH ₂	J37	0	CH
10	237	OMe	OMe	A1	COOH	CH ₂	J39	0	CH
	238	OMe	OMe	A1	COOH	CH ₂	J50	0	CH
	239	OMe	OMe	A1	COOH	CH ₂	J63	0	CH
	240	OMe	OMe	A1	COOH	CH ₂	J64	0	CH
	241	OMe	OMe	A1	COOH	CH ₂	J65	0	CH
15	242	OMe	OMe	A1	COOH	CH ₂	J67	0	CH
	243	OMe	OMe	A1	COOH	CH ₂	J71	0	CH
	244	F	F	A1	COOH	CH ₂	J35	0	CH
	245	F	F	A1	COOH	CH ₂	J37	0	CH
	246	F	F	A1	COOH	CH ₂	J39	0	CH
20	247	F	F	A1	COOH	CH ₂	J50	0	CH
	248	F	F	A1	COOH	CH ₂	J63	0	CH
	249	F	F	A1	COOH	CH ₂	J64	0	CH
	250	F	F	A1	COOH	CH ₂	J65	0	CH

Table 11

	Compound No.	R ¹	R ²	A	E	G	J	m	X
35	251	F	F	A1	COOH	CH ₂	J67	0	CH
	252	H	H	A1	COOH	CH ₂	J35	0	N
	253	H	H	A1	COOH	CH ₂	J37	0	N
	254	H	H	A1	COOH	CH ₂	J39	0	N
	255	H	H	A1	COOH	CH ₂	J50	0	N
40	256	H	H	A1	COOH	CH ₂	J63	0	N
	257	H	H	A1	COOH	CH ₂	J64	0	N
	258	H	H	A1	COOH	CH ₂	J65	0	N
	259	H	H	A1	COOH	CH ₂	J67	0	N
	260	Me	H	A1	COOH	CH ₂	J35	0	CH
45	261	Me	H	A1	COOH	CH ₂	J37	0	CH
	262	Me	H	A1	COOH	CH ₂	J39	0	CH
	263	Me	H	A1	COOH	CH ₂	J50	0	CH
	264	Me	H	A1	COOH	CH ₂	J63	0	CH
	265	Me	H	A1	COOH	CH ₂	J64	0	CH
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55									

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Table 11 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	266	Me	H	A1	COOH	CH ₂	J65	0	CH
	267	Me	H	A1	COOH	CH ₂	J67	0	CH
	268	OMe	H	A1	COOH	CH ₂	J35	0	CH
	269	OMe	H	A1	COOH	CH ₂	J37	0	CH
10	270	OMe	H	A1	COOH	CH ₂	J39	0	CH
	271	OMe	H	A1	COOH	CH ₂	J50	0	CH
	272	OMe	H	A1	COOH	CH ₂	J63	0	CH
	273	OMe	H	A1	COOH	CH ₂	J64	0	CH
15	274	OMe	H	A1	COOH	CH ₂	J65	0	CH
	275	OMe	H	A1	COOH	CH ₂	J67	0	CH

20

Table 12

	Compound No.	R ¹	R ²	A	E	G	J	m	X
25	276	OEt	H	A1	COOH	CH ₂	J63	0	CH
	277	OEt	H	A1	COOH	CH ₂	J64	0	CH
	278	OEt	H	A1	COOH	CH ₂	J65	0	CH
	279	CF ₃	H	A1	COOH	CH ₂	J63	0	CH
30	280	CF ₃	H	A1	COOH	CH ₂	J64	0	CH
	281	CF ₃	H	A1	COOH	CH ₂	J65	0	CH
	282	CN	H	A1	COOH	CH ₂	J63	0	CH
	283	CN	H	A1	COOH	CH ₂	J64	0	CH
35	284	CN	H	A1	COOH	CH ₂	J65	0	CH
	285	Cl	H	A1	COOH	CH ₂	J63	0	N
	286	Cl	H	A1	COOH	CH ₂	J64	0	N
	287	Cl	H	A1	COOH	CH ₂	J65	0	N
40	288	Me	Me	A2	COOH	CH ₂	J35	0	CH
	289	Me	Me	A2	COOH	CH ₂	J37	0	CH
	290	Me	Me	A2	COOH	CH ₂	J39	0	CH
	291	Me	Me	A2	COOH	CH ₂	J63	0	CH
45	292	Me	Me	A2	COOH	CH ₂	J64	0	CH
	293	Me	Me	A2	COOH	CH ₂	J65	0	CH
	294	Me	Me	A2	COOH	CH ₂ CH ₂	J1	0	CH
	295	Me	Me	A3	COOH	CH ₂	J1	0	CH
50	296	Me	Me	A3	COOH	CH ₂	J35	0	CH
	297	Me	Me	A3	COOH	CH ₂	J37	0	CH
	298	Me	Me	A3	COOH	CH ₂	J39	0	CH
	299	Me	Me	A3	COOH	CH ₂	J50	0	CH

Table 12 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
300	Me	Me	A3	COOH	CH ₂	J63	0	CH

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Table 13

Compound No.	R ¹	R ²	A	E	G	J	m	X
301	Me	Me	A3	COOH	CH ₂	J64	0	CH
302	Me	Me	A3	COOH	CH ₂	J65	0	CH
303	Me	Me	A3	COOH	CH ₂	J67	0	CH
304	Me	Me	A3	COOH	CH ₂ CH ₂	J1	0	CH
305	Me	Me	A3	COOH	CH ₂ CH ₂	J63	0	CH
306	Me	Me	A4	COOH	CH ₂	J1	0	CH
307	Me	Me	A4	COOH	CH ₂	J35	0	CH
308	Me	Me	A4	COOH	CH ₂	J37	0	CH
309	Me	Me	A4	COOH	CH ₂	J39	0	CH
310	Me	Me	A4	COOH	CH ₂	J50	0	CH
311	Me	Me	A4	COOH	CH ₂	J63	0	CH
312	Me	Me	A4	COOH	CH ₂	J64	0	CH
313	Me	Me	A4	COOH	CH ₂	J65	0	CH
314	Me	Me	A4	COOH	CH ₂	J67	0	CH
315	Me	Me	A4	COOH	CH ₂ CH ₂	J1	0	CH
316	Me	Me	A4	COOH	CH ₂ CH ₂	J63	0	CH
317	H	H	A4	COOH	CH ₂	J37	0	CH
318	H	H	A4	COOH	CH ₂	J39	0	CH
319	H	H	A4	COOH	CH ₂	J63	0	CH
320	H	H	A4	COOH	CH ₂	J64	0	CH
321	H	H	A4	COOH	CH ₂	J65	0	CH
322	Cl	Cl	A4	COOH	CH ₂	J37	0	CH
323	Cl	Cl	A4	COOH	CH ₂	J39	0	CH
324	Cl	Cl	A4	COOH	CH ₂	J63	0	CH
325	Cl	Cl	A4	COOH	CH ₂	J64	0	CH

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Table 14

Compound No.	R ¹	R ²	A	E	G	J	m	X
326	Cl	Cl	A4	COOH	CH ₂	J65	0	CH
327	H	H	A4	COOH	CH ₂	J37	0	N
328	H	H	A4	COOH	CH ₂	J39	0	N

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Table 14 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	329	H	H	A4	COOH	CH ₂	J63	0	N
	330	H	H	A4	COOH	CH ₂	J64	0	N
	331	H	H	A4	COOH	CH ₂	J65	0	N
10	332	Me	Me	A5	COOH	CH ₂	J1	0	CH
	333	Me	Me	A5	COOH	CH ₂ CH ₂	J1	0	CH
	334	Me	Me	A6	COOH	CH ₂	J1	0	CH
15	335	Me	Me	A6	COOH	CH ₂ CH ₂	J1	0	CH
	336	Me	Me	A7	COOH	CH ₂	J1	0	CH
	337	Me	Me	A7	COOH	CH ₂ CH ₂	J1	0	CH
20	338	Me	Me	A8	COOH	CH ₂	J1	0	CH
	339	Me	Me	A8	COOH	CH ₂ CH ₂	J1	0	CH
	340	Me	Me	A9	COOH	CH ₂	J1	0	CH
25	341	Me	Me	A9	COOH	CH ₂ CH ₂	J1	0	CH
	342	Me	Me	A10	COOH	CH ₂	J1	0	CH
	343	Me	Me	A10	COOH	CH ₂ CH ₂	J1	0	CH
30	344	Me	Me	A11	COOH	CH ₂	J37	0	CH
	345	Me	Me	A11	COOH	CH ₂	J39	0	CH
	346	Me	Me	A11	COOH	CH ₂	J50	0	CH
35	347	Me	Me	A11	COOH	CH ₂	J63	0	CH
	348	Me	Me	A11	COOH	CH ₂	J64	0	CH
	349	H	H	A11	COOH	CH ₂	J37	0	CH
35	350	H	H	A11	COOH	CH ₂	J39	0	CH

Table 15

	Compound No.	R ¹	R ²	A	E	G	J	m	X
40	351	H	H	A11	COOH	CH ₂	J50	0	CH
	352	H	H	A11	COOH	CH ₂	J63	0	CH
	353	H	H	A11	COOH	CH ₂	J64	0	CH
45	354	H	H	A11	COOH	CH ₂	J65	0	CH
	355	Cl	Cl	A11	COOH	CH ₂	J37	0	CH
	356	Cl	Cl	A11	COOH	CH ₂	J39	0	CH
50	357	Cl	Cl	A11	COOH	CH ₂	J50	0	CH
	358	Cl	Cl	A11	COOH	CH ₂	J63	0	CH
	359	Cl	Cl	A11	COOH	CH ₂	J64	0	CH
55	360	Cl	Cl	A11	COOH	CH ₂	J65	0	CH
	361	H	H	A11	COOH	CH ₂	J37	0	N

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Table 15 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	362	H	H	A11	COOH	CH ₂	J39	0	N
	363	H	H	A11	COOH	CH ₂	J50	0	N
	364	H	H	A11	COOH	CH ₂	J63	0	N
	365	H	H	A11	COOH	CH ₂	J64	0	N
10	366	H	H	A11	COOH	CH ₂	J65	0	N
	367	Me	Me	A12	COOH	CH ₂	J1	0	CH
	368	Me	Me	A12	COOH	CH ₂ CH ₂	J1	0	CH
	369	Me	Me	A13	COOH	CH ₂	J1	0	CH
15	370	Me	Me	A13	COOH	CH ₂ CH ₂	J1	0	CH
	371	Me	Me	A14	COOH	CH ₂	J1	0	CH
	372	Me	Me	A14	COOH	CH ₂ CH ₂	J1	0	CH
	373	Me	Me	A15	COOH	CH ₂	J1	0	CH
20	374	Me	Me	A15	COOH	CH ₂ CH ₂	J1	0	CH
	375	Me	Me	A16	COOH	CH ₂	J1	0	CH

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Table 16

	Compound No.	R ¹	R ²	A	E	G	J	m	X
30	376	Me	Me	A16	COOH	CH ₂ CH ₂	J1	0	CH
	377	Me	Me	A16	COOH	CH ₂	J37	0	CH
	378	Me	Me	A16	COOH	CH ₂	J39	0	CH
	379	Me	Me	A16	COOH	CH ₂	J50	0	CH
35	380	Me	Me	A16	COOH	CH ₂	J63	0	CH
	381	Me	Me	A16	COOH	CH ₂	J64	0	CH
	382	Me	Me	A16	COOH	CH ₂	J65	0	CH
	383	H	H	A16	COOH	CH ₂	J37	0	CH
40	384	H	H	A16	COOH	CH ₂	J39	0	CH
	385	H	H	A16	COOH	CH ₂	J50	0	CH
	386	H	H	A16	COOH	CH ₂	J63	0	CH
	387	H	H	A16	COOH	CH ₂	J64	0	CH
45	388	H	H	A16	COOH	CH ₂	J65	0	CH
	389	Me	Me	A17	COOH	CH ₂	J1	0	CH
	390	Me	Me	A17	COOH	CH ₂ CH ₂	J1	0	CH
	391	Me	Me	A18	COOH	CH ₂ CH ₂	J1	0	CH
50	392	Me	Me	A18	COOH	CH ₂	J37	0	CH
	393	Me	Me	A18	COOH	CH ₂	J39	0	CH
	394	Me	Me	A18	COOH	CH ₂	J50	0	CH
	395	Me	Me	A18	COOH	CH ₂	J63	0	CH

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Table 16 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
396	Me	Me	A18	COOH	CH ₂	J64	0	CH
397	Me	Me	A18	COOH	CH ₂	J65	0	CH
398	H	H	A18	COOH	CH ₂	J37	0	CH
399	H	H	A18	COOH	CH ₂	J39	0	CH
400	H	H	A18	COOH	CH ₂	J50	0	CH

Table 17

Compound No.	R ¹	R ²	A	E	G	J	m	X
401	H	H	A18	COOH	CH ₂	J63	0	CH
402	H	H	A18	COOH	CH ₂	J64	0	CH
403	H	H	A18	COOH	CH ₂	J65	0	CH
404	Cl	Cl	A18	COOH	CH ₂	J37	0	CH
405	Cl	Cl	A18	COOH	CH ₂	J63	0	CH
406	Cl	Cl	A18	COOH	CH ₂	J64	0	CH
407	Cl	Cl	A18	COOH	CH ₂	J65	0	CH
408	H	H	A18	COOH	CH ₂	J37	0	N
409	H	H	A18	COOH	CH ₂	J39	0	N
410	H	H	A18	COOH	CH ₂	J63	0	N
411	H	H	A18	COOH	CH ₂	J64	0	N
412	H	H	A18	COOH	CH ₂	J65	0	N
413	Me	H	A18	COOH	CH ₂	J37	0	CH
414	Me	H	A18	COOH	CH ₂	J39	0	CH
415	Me	H	A18	COOH	CH ₂	J63	0	CH
416	Me	H	A18	COOH	CH ₂	J64	0	CH
417	Me	H	A18	COOH	CH ₂	J65	0	CH
418	OMe	H	A18	COOH	CH ₂	J37	0	CH
419	OMe	H	A18	COOH	CH ₂	J39	0	CH
420	OMe	H	A18	COOH	CH ₂	J63	0	CH
421	OMe	H	A18	COOH	CH ₂	J64	0	CH
422	OMe	H	A18	COOH	CH ₂	J65	0	CH
423	OEt	H	A18	COOH	CH ₂	J63	0	CH
424	OEt	H	A18	COOH	CH ₂	J64	0	CH
425	OEt	H	A18	COOH	CH ₂	J65	0	CH

Table 18

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	426	CF ₃	H	A18	COOH	CH ₂	J63	0	CH
	427	CF ₃	H	A18	COOH	CH ₂	J64	0	CH
10	428	CF ₃	H	A18	COOH	CH ₂	J65	0	CH
	429	CN	H	A18	COOH	CH ₂	J63	0	CH
15	430	CN	H	A18	COOH	CH ₂	J64	0	CH
	431	CN	H	A18	COOH	CH ₂	J65	0	CH
20	432	F	H	A18	COOH	CH ₂	J63	0	CH
	433	F	H	A18	COOH	CH ₂	J64	0	CH
25	434	F	H	A18	COOH	CH ₂	J65	0	CH
	435	Cl	H	A18	COOH	CH ₂	J63	0	N
30	436	Cl	H	A18	COOH	CH ₂	J64	0	N
	437	Cl	H	A18	COOH	CH ₂	J65	0	N
35	438	H	H	A18	COOH	CH ₂	J37	0	N
	439	Me	Me	A19	COOH	CH ₂	J1	0	CH
40	440	Me	Me	A19	COOH	CH ₂ CH ₂	J1	0	CH
	441	Me	Me	A19	COOH	CH ₂	J37	0	CH
45	442	Me	Me	A19	COOH	CH ₂	J39	0	CH
	443	Me	Me	A19	COOH	CH ₂	J50	0	CH
50	444	Me	Me	A19	COOH	CH ₂	J63	0	CH
	445	Me	Me	A19	COOH	CH ₂	J64	0	CH
55	446	Me	Me	A19	COOH	CH ₂	J65	0	CH
	447	H	H	A19	COOH	CH ₂	J1	0	CH
55	448	H	H	A19	COOH	CH ₂ CH ₂	J1	0	CH
	449	H	H	A19	COOH	CH ₂	J37	0	CH
	450	H	H	A19	COOH	CH ₂	J39	0	CH

Table 19

	Compound No.	R ¹	R ²	A	E	G	J	m	X
50	451	H	H	A19	COOH	CH ₂	J50	0	CH
	452	H	H	A19	COOH	CH ₂	J63	0	CH
55	453	H	H	A19	COOH	CH ₂	J64	0	CH
	454	H	H	A19	COOH	CH ₂	J65	0	CH
55	455	Me	Me	A20	COOH	CH ₂	J64	0	CH
	456	Me	Me	A20	COOH	CH ₂	J65	0	CH
	457	Me	Me	A20	COOH	CH ₂	J67	0	CH

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Table 19 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	458	Me	Me	A20	COOH	CH ₂	J71	0	CH
	459	H	H	A20	COOH	CH ₂	J64	0	CH
	460	H	H	A20	COOH	CH ₂	J65	0	CH
	461	H	H	A20	COOH	CH ₂	J67	0	CH
	462	H	H	A20	COOH	CH ₂	J71	0	CH
10	463	Cl	Cl	A20	COOH	CH ₂	J64	0	CH
	464	Cl	Cl	A20	COOH	CH ₂	J65	0	CH
	465	Cl	Cl	A20	COOH	CH ₂	J67	0	CH
	466	Cl	Cl	A20	COOH	CH ₂	J71	0	CH
	467	H	H	A20	COOH	CH ₂	J64	0	N
15	468	H	H	A20	COOH	CH ₂	J65	0	N
	469	H	H	A20	COOH	CH ₂	J67	0	N
	470	H	H	A20	COOH	CH ₂	J71	0	N
	471	Me	H	A20	COOH	CH ₂	J64	0	CH
	472	Me	H	A20	COOH	CH ₂	J65	0	CH
20	473	Me	H	A20	COOH	CH ₂	J67	0	CH
	474	Me	H	A20	COOH	CH ₂	J71	0	CH
	475	OMe	H	A20	COOH	CH ₂	J64	0	CH

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Table 20

	Compound No.	R ¹	R ²	A	E	G	J	m	X
35	476	OMe	H	A20	COOH	CH ₂	J65	0	CH
	477	OMe	H	A20	COOH	CH ₂	J67	0	CH
	478	OMe	H	A20	COOH	CH ₂	J71	0	CH
	479	OEt	H	A20	COOH	CH ₂	J64	0	CH
	480	OEt	H	A20	COOH	CH ₂	J65	0	CH
40	481	OEt	H	A20	COOH	CH ₂	J67	0	CH
	482	OEt	H	A20	COOH	CH ₂	J71	0	CH
	483	F	H	A20	COOH	CH ₂	J64	0	CH
	484	F	H	A20	COOH	CH ₂	J65	0	CH
	485	F	H	A20	COOH	CH ₂	J67	0	CH
45	486	F	H	A20	COOH	CH ₂	J71	0	CH
	487	CF ₃	H	A20	COOH	CH ₂	J64	0	CH
	488	CF ₃	H	A20	COOH	CH ₂	J65	0	CH
	489	CF ₃	H	A20	COOH	CH ₂	J67	0	CH
	490	CF ₃	H	A20	COOH	CH ₂	J71	0	CH

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Table 20 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	491	CN	H	A20	COOH	CH ₂	J64	0	CH
	492	CN	H	A20	COOH	CH ₂	J65	0	CH
	493	CN	H	A20	COOH	CH ₂	J67	0	CH
	494	CN	H	A20	COOH	CH ₂	J71	0	CH
10	495	Cl	H	A20	COOH	CH ₂	J64	0	N
	496	Cl	H	A20	COOH	CH ₂	J65	0	N
	497	Cl	H	A20	COOH	CH ₂	J67	0	N
	498	Cl	H	A20	COOH	CH ₂	J71	0	N
15	499	H	H	A21	COOH	CH ₂	J63	0	CH
	500	H	H	A21	COOH	CH ₂	J65	0	CH

20

Table 21

	Compound No.	R ¹	R ²	A	E	G	J	m	X
25	501	Me	Me	A1	COOH	CH ₂ CH ₂	J1	0	CH
	502	Me	Me	A1	COOH	CH ₂ CH ₂	J37	0	CH
	503	Me	Me	A1	COOH	CH ₂ CH ₂	J39	0	CH
	504	Me	Me	A1	COOH	CH ₂ CH ₂	J50	0	CH
30	505	Me	Me	A1	COOH	CH ₂ CH ₂	J62	0	CH
	506	Me	Me	A1	COOH	CH ₂ CH ₂	J63	0	CH
	507	Me	Me	A1	COOH	CH ₂ CH ₂	J64	0	CH
	508	Me	Me	A1	COOH	CH ₂ CH ₂	J65	0	CH
35	509	H	H	A1	COOH	CH ₂ CH ₂	J1	0	CH
	510	H	H	A1	COOH	CH ₂ CH ₂	J37	0	CH
	511	H	H	A1	COOH	CH ₂ CH ₂	J39	0	CH
	512	H	H	A1	COOH	CH ₂ CH ₂	J50	0	CH
40	513	H	H	A1	COOH	CH ₂ CH ₂	J62	0	CH
	514	H	H	A1	COOH	CH ₂ CH ₂	J63	0	CH
	515	H	H	A1	COOH	CH ₂ CH ₂	J64	0	CH
	516	H	H	A1	COOH	CH ₂ CH ₂	J65	0	CH
45	517	Me	Me	A4	COOH	CH ₂ CH ₂	J37	0	CH
	518	Me	Me	A4	COOH	CH ₂ CH ₂	J39	0	CH
	519	Me	Me	A4	COOH	CH ₂ CH ₂	J67	0	CH
	520	Me	Me	A4	COOH	CH ₂ CH ₂	J64	0	CH
50	521	Me	Me	A4	COOH	CH ₂ CH ₂	J65	0	CH
	522	H	H	A4	COOH	CH ₂ CH ₂	J37	0	CH
	523	H	H	A4	COOH	CH ₂ CH ₂	J39	0	CH
	524	H	H	A4	COOH	CH ₂ CH ₂	J63	0	CH

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Table 21 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
525	H	H	A4	COOH	CH ₂ CH ₂	J64	0	CH

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Table 22

Compound No.	R ¹	R ²	A	E	G	J	m	X
526	H	H	A4	COOH	CH ₂ CH ₂	J65	0	CH
527	H	H	A11	COOH	CH ₂ CH ₂	J37	0	CH
528	H	H	A11	COOH	CH ₂ CH ₂	J39	0	CH
529	H	H	A11	COOH	CH ₂ CH ₂	J63	0	CH
530	H	H	A11	COOH	CH ₂ CH ₂	J64	0	CH
531	H	H	A11	COOH	CH ₂ CH ₂	J65	0	CH
532	H	H	A18	COOH	CH ₂ CH ₂	J37	0	CH
533	H	H	A18	COOH	CH ₂ CH ₂	J39	0	CH
534	H	H	A18	COOH	CH ₂ CH ₂	J63	0	CH
535	H	H	A18	COOH	CH ₂ CH ₂	J64	0	CH
536	H	H	A18	COOH	CH ₂ CH ₂	J65	0	CH
537	Me	Me	A20	COOH	CH ₂ CH ₂	J37	0	CH
538	Me	Me	A20	COOH	CH ₂ CH ₂	J39	0	CH
539	Me	Me	A20	COOH	CH ₂ CH ₂	J63	0	CH
540	Me	Me	A20	COOH	CH ₂ CH ₂	J64	0	CH
541	Me	Me	A20	COOH	CH ₂ CH ₂	J65	0	CH
542	H	H	A20	COOH	CH ₂ CH ₂	J37	0	CH
543	H	H	A20	COOH	CH ₂ CH ₂	J39	0	CH
544	H	H	A20	COOH	CH ₂ CH ₂	J63	0	CH
545	H	H	A20	COOH	CH ₂ CH ₂	J64	0	CH
546	H	H	A20	COOH	CH ₂ CH ₂	J65	0	CH
547	Me	Me	A1	COOH	CO	J1	0	CH
548	Me	Me	A1	COOH	CO	J63	0	CH
549	H	H	A1	COOH	CO	J1	0	CH
550	H	H	A1	COOH	CO	J63	0	CH

50

Table 23

Compound No.	R ¹	R ²	A	E	G	J	m	X
551	Me	Me	A4	COOH	CO	J1	0	CH
552	Me	Me	A4	COOH	CO	J63	0	CH
553	H	H	A4	COOH	CO	J1	0	CH

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Table 23 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	554	H	H	A4	COOH	CO	J63	0	CH
	555	H	H	A11	COOH	CO	J1	0	CH
	556	H	H	A11	COOH	CO	J63	0	CH
	557	H	H	A18	COOH	CO	J1	0	CH
	558	H	H	A18	COOH	CO	J63	0	CH
10	559	H	H	A20	COOH	CO	J1	0	CH
	560	H	H	A20	COOH	CO	J63	0	CH
	561	Me	Me	A1	COOH	SO ₂	J1	0	CH
	562	Me	Me	A1	COOH	SO ₂	J63	0	CH
	563	H	H	A1	COOH	SO ₂	J1	0	CH
15	564	H	H	A1	COOH	SO ₂	J63	0	CH
	565	H	H	A4	COOH	SO ₂	J1	0	CH
	566	H	H	A4	COOH	SO ₂	J63	0	CH
	567	H	H	A11	COOH	SO ₂	J1	0	CH
	568	H	H	A11	COOH	SO ₂	J63	0	CH
20	569	H	H	A18	COOH	SO ₂	J1	0	CH
	570	H	H	A18	COOH	SO ₂	J63	0	CH
	571	H	H	A20	COOH	SO ₂	J1	0	CH
	572	H	H	A20	COOH	SO ₂	J63	0	CH
	573	H	H	A1	COOH	CH ₂ CO	J1	0	CH
25	574	H	H	A1	COOH	CH ₂ CO	J2	0	CH
	575	H	H	A1	COOH	CH ₂ CO	J3	0	CH
30									
35									

Table 24

	Compound No.	R ¹	R ²	A	E	G	J	m	X
40	576	H	H	A1	COOH	CH ₂ CO	J4	0	CH
	577	H	H	A1	COOH	CH ₂ CO	J5	0	CH
	578	H	H	A1	COOH	CH ₂ CO	J6	0	CH
	579	H	H	A1	COOH	CH ₂ CO	J7	0	CH
	580	H	H	A1	COOH	CH ₂ CO	J8	0	CH
45	581	H	H	A1	COOH	CH ₂ CO	J9	0	CH
	582	H	H	A1	COOH	CH ₂ CO	J10	0	CH
	583	H	H	A1	COOH	CH ₂ CO	J11	0	CH
	584	H	H	A1	COOH	CH ₂ CO	J12	0	CH
	585	H	H	A1	COOH	CH ₂ CO	J13	0	CH
50	586	H	H	A1	COOH	CH ₂ CO	J17	0	CH
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Table 24 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	587	H	H	A1	COOH	CH ₂ CO	J18	0	CH
	588	H	H	A1	COOH	CH ₂ CO	J19	0	CH
	589	H	H	A1	COOH	CH ₂ CO	J23	0	CH
10	590	H	H	A1	COOH	CH ₂ CO	J24	0	CH
	591	H	H	A1	COOH	CH ₂ CO	J25	0	CH
	592	H	H	A1	COOH	CH ₂ CO	J36	0	CH
15	593	H	H	A1	COOH	CH ₂ CO	J47	0	CH
	594	H	H	A1	COOH	CH ₂ CO	J57	0	CH
	595	H	H	A1	COOH	CH ₂ CO	J62	0	CH
20	596	Me	Me	A1	COOH	CH ₂ CO	J1	0	CH
	597	Me	Me	A1	COOH	CH ₂ CO	J2	0	CH
	598	Me	Me	A1	COOH	CH ₂ CO	J3	0	CH
25	599	Me	Me	A1	COOH	CH ₂ CO	J4	0	CH
	600	Me	Me	A1	COOH	CH ₂ CO	J5	0	CH

Table 25

	Compound No.	R ¹	R ²	A	E	G	J	m	X
30	601	Me	Me	A1	COOH	CH ₂ CO	J6	0	CH
	602	Me	Me	A1	COOH	CH ₂ CO	J7	0	CH
	603	Me	Me	A1	COOH	CH ₂ CO	J8	0	CH
35	604	Me	Me	A1	COOH	CH ₂ CO	J9	0	CH
	605	Me	Me	A1	COOH	CH ₂ CO	J10	0	CH
	606	Me	Me	A1	COOH	CH ₂ CO	J11	0	CH
40	607	Me	Me	A1	COOH	CH ₂ CO	J12	0	CH
	608	Me	Me	A1	COOH	CH ₂ CO	J13	0	CH
	609	Me	Me	A1	COOH	CH ₂ CO	J17	0	CH
45	610	Me	Me	A1	COOH	CH ₂ CO	J18	0	CH
	611	Me	Me	A1	COOH	CH ₂ CO	J19	0	CH
	612	Me	Me	A1	COOH	CH ₂ CO	J23	0	CH
50	613	Me	Me	A1	COOH	CH ₂ CO	J24	0	CH
	614	Me	Me	A1	COOH	CH ₂ CO	J25	0	CH
	615	Me	Me	A1	COOH	CH ₂ CO	J36	0	CH
55	616	Me	Me	A1	COOH	CH ₂ CO	J47	0	CH
	617	Me	Me	A1	COOH	CH ₂ CO	J57	0	CH
	618	Me	Me	A1	COOH	CH ₂ CO	J62	0	CH
60	619	H	H	A1	COOH	CH ₂ CONH	J1	0	CH
	620	H	H	A1	COOH	CH ₂ CONH	J2	0	CH

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Table 25 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
621	H	H	A1	COOH	CH ₂ CONH	J3	0	CH
622	H	H	A1	COOH	CH ₂ CONH	J4	0	CH
623	H	H	A1	COOH	CH ₂ CONH	J5	0	CH
624	H	H	A1	COOH	CH ₂ CONH	J6	0	CH
625	H	H	A1	COOH	CH ₂ CONH	J7	0	CH

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Table 26

Compound No.	R ¹	R ²	A	E	G	J	m	X
626	H	H	A1	COOH	CH ₂ CONH	J8	0	CH
627	H	H	A1	COOH	CH ₂ CONH	J9	0	CH
628	H	H	A1	COOH	CH ₂ CONH	J10	0	CH
629	H	H	A1	COOH	CH ₂ CONH	J11	0	CH
630	H	H	A1	COOH	CH ₂ CONH	J12	0	CH
631	H	H	A1	COOH	CH ₂ CONH	J13	0	CH
632	H	H	A1	COOH	CH ₂ CONH	J14	0	CH
633	H	H	A1	COOH	CH ₂ CONH	J15	0	CH
634	H	H	A1	COOH	CH ₂ CONH	J16	0	CH
635	H	H	A1	COOH	CH ₂ CONH	J17	0	CH
636	H	H	A1	COOH	CH ₂ CONH	J18	0	CH
637	H	H	A1	COOH	CH ₂ CONH	J19	0	CH
638	H	H	A1	COOH	CH ₂ CONH	J20	0	CH
639	H	H	A1	COOH	CH ₂ CONH	J21	0	CH
640	H	H	A1	COOH	CH ₂ CONH	J22	0	CH
641	H	H	A1	COOH	CH ₂ CONH	J23	0	CH
642	H	H	A1	COOH	CH ₂ CONH	J24	0	CH
643	H	H	A1	COOH	CH ₂ CONH	J25	0	CH
644	H	H	A1	COOH	CH ₂ CONH	J26	0	CH
645	H	H	A1	COOH	CH ₂ CONH	J27	0	CH
646	H	H	A1	COOH	CH ₂ CONH	J28	0	CH
647	H	H	A1	COOH	CH ₂ CONH	J29	0	CH
648	H	H	A1	COOH	CH ₂ CONH	J30	0	CH
649	H	H	A1	COOK	CH ₂ CONH	J31	0	CH
650	H	H	A1	COOH	CH ₂ CONH	J32	0	CH

Table 27

Compound No.	R ¹	R ²	A	E	G	J	m	X
651	H	H	A1	COOH	CH ₂ CONH	J33	0	CH
652	H	H	A1	COOH	CH ₂ CONH	J34	0	CH
653	H	H	A1	COOH	CH ₂ CONH	J35	0	CH
654	H	H	A1	COOH	CH ₂ CONH	J37	0	CH
655	H	H	A1	COOH	CH ₂ CONH	J39	0	CH
656	H	H	A1	COOH	CH ₂ CONH	J62	0	CH
657	H	H	A1	COOH	CH ₂ CONH	J63	0	CH
658	Me	Me	A1	COOH	CH ₂ CONH	J1	0	CH
659	Me	Me	A1	COOH	CH ₂ CONH	J2	0	CH
660	Me	Me	A1	COOH	CH ₂ CONH	J3	0	CH
661	Me	Me	A1	COOH	CH ₂ CONH	J4	0	CH
662	Me	Me	A1	COOH	CH ₂ CONH	J5	0	CH
663	Me	Me	A1	COOH	CH ₂ CONH	J6	0	CH
664	Me	Me	A1	COOH	CH ₂ CONH	J7	0	CH
665	Me	Me	A1	COOH	CH ₂ CONH	J8	0	CH
666	Me	Me	A1	COOH	CH ₂ CONH	J9	0	CH
667	Me	Me	A1	COOH	CH ₂ CONH	J10	0	CH
668	Me	Me	A1	COOH	CH ₂ CONH	J11	0	CH
669	Me	Me	A1	COOH	CH ₂ CONH	J12	0	CH
670	Me	Me	A1	COOH	CH ₂ CONH	J13	0	CH
671	Me	Me	A1	COOH	CH ₂ CONH	J14	0	CH
672	Me	Me	A1	COOH	CH ₂ CONH	J15	0	CH
673	Me	Me	A1	COOH	CH ₂ CONH	J16	0	CH
674	Me	Me	A1	COOH	CH ₂ CONH	J17	0	CH
675	Me	Me	A1	COOH	CH ₂ CONH	J18	0	CH

Table 28

Compound No.	R ¹	R ²	A	E	G	J	m	X
676	Me	Me	A1	COOH	CH ₂ CONH	J19	0	CH
677	Me	Me	A1	COOH	CH ₂ CONH	J20	0	CH
678	Me	Me	A1	COOH	CH ₂ CONH	J21	0	CH
679	Me	Me	A1	COOH	CH ₂ CONH	J22	0	CH
680	Me	Me	A1	COOH	CH ₂ CONH	J23	0	CH
681	Me	Me	A1	COOH	CH ₂ CONH	J24	0	CH
682	Me	Me	A1	COOH	CH ₂ CONH	J25	0	CH

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Table 28 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	683	Me	Me	A1	COOH	CH ₂ CONH	J26	0	CH
10	684	Me	Me	A1	COOH	CH ₂ CONH	J27	0	CH
15	685	Me	Me	A1	COOH	CH ₂ CONH	J28	0	CH
20	686	Me	Me	A1	COOH	CH ₂ CONH	J29	0	CH
25	687	Me	Me	A1	COOH	CH ₂ CONH	J30	0	CH
30	688	Me	Me	A1	COOH	CH ₂ CONH	J31	0	CH
35	689	Me	Me	A1	COOH	CH ₂ CONH	J32	0	CH
40	690	Me	Me	A1	COOH	CH ₂ CONH	J33	0	CH
45	691	Me	Me	A1	COOH	CH ₂ CONH	J34	0	CH
50	692	Me	Me	A1	COOH	CH ₂ CONH	J35	0	CH
55	693	Me	Me	A1	COOH	CH ₂ CONH	J37	0	CH
60	694	Me	Me	A1	COOH	CH ₂ CONH	J39	0	CH
65	695	Me	Me	A1	COOH	CH ₂ CONH	J62	0	CH
70	696	Me	Me	A1	COOH	CH ₂ CONH	J63	0	CH
75	697	H	H	A1	COOH	CH ₂ CH ₂ O	J1	0	CH
80	698	H	H	A1	COOH	CH ₂ CH ₂ O	J2	0	CH
85	699	H	H	A1	COOH	CH ₂ CH ₂ O	J3	0	CH
90	700	H	H	A1	COOH	CH ₂ CH ₂ O	J4	0	CH

Table 29

	Compound No.	R ¹	R ²	A	E	G	J	m	X
35	701	H	H	A1	COOH	CH ₂ CH ₂ O	J5	0	CH
40	702	H	H	A1	COOH	CH ₂ CH ₂ O	J6	0	CH
45	703	H	H	A1	COOH	CH ₂ CH ₂ O	J7	0	CH
50	704	H	H	A1	COOH	CH ₂ CH ₂ O	J8	0	CH
55	705	H	H	A1	COOH	CH ₂ CH ₂ O	J9	0	CH
60	706	H	H	A1	COOH	CH ₂ CH ₂ O	J10	0	CH
65	707	H	H	A1	COOH	CH ₂ CH ₂ O	J11	0	CH
70	708	H	H	A1	COOH	CH ₂ CH ₂ O	J12	0	CH
75	709	H	H	A1	COOH	CH ₂ CH ₂ O	J13	0	CH
80	710	H	H	A1	COOH	CH ₂ CH ₂ O	J14	0	CH
85	711	H	H	A1	COOH	CH ₂ CH ₂ O	J15	0	CH
90	712	H	H	A1	COOH	CH ₂ CH ₂ O	J16	0	CH
95	713	H	H	A1	COOH	CH ₂ CH ₂ O	J17	0	CH
100	714	H	H	A1	COOH	CH ₂ CH ₂ O	J18	0	CH
105	715	H	H	A1	COOH	CH ₂ CH ₂ O	J19	0	CH

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Table 29 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
716	H	H	A1	COOH	CH ₂ CH ₂ O	J20	0	CH
717	H	H	A1	COOH	CH ₂ CH ₂ O	J21	0	CH
718	H	H	A1	COOH	CH ₂ CH ₂ O	J22	0	CH
719	H	H	A1	COOH	CH ₂ CH ₂ O	J23	0	CH
720	H	H	A1	COOH	CH ₂ CH ₂ O	J24	0	CH
721	H	H	A1	COOH	CH ₂ CH ₂ O	J25	0	CH
722	H	H	A1	COOH	CH ₂ CH ₂ O	J26	0	CH
723	H	H	A1	COOH	CH ₂ CH ₂ O	J27	0	CH
724	H	H	A1	COOH	CH ₂ CH ₂ O	J28	0	CH
725	H	H	A1	COOH	CH ₂ CH ₂ O	J29	0	CH

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Table 30

Compound No.	R ¹	R ²	A	E	G	J	m	X
726	H	H	A1	COOH	CH ₂ CH ₂ O	J30	0	CH
727	H	H	A1	COOH	CH ₂ CH ₂ O	J31	0	CH
728	H	H	A1	COOH	CH ₂ CH ₂ O	J32	0	CH
729	H	H	A1	COOH	CH ₂ CH ₂ O	J33	0	CH
730	H	H	A1	COOH	CH ₂ CH ₂ O	J34	0	CH
731	H	H	A1	COOH	CH ₂ CH ₂ O	J35	0	CH
732	H	H	A1	COOH	CH ₂ CH ₂ O	J37	0	CH
733	H	H	A1	COOH	CH ₂ CH ₂ O	J39	0	CH
734	H	H	A1	COOH	CH ₂ CH ₂ O	J62	0	CH
735	H	H	A1	COOH	CH ₂ CH ₂ O	J63	0	CH
736	Me	Me	A1	COOH	CH ₂ CH ₂ O	J1	c	CH
737	Me	Me	A1	COOH	CH ₂ CH ₂ O	J2	0	CH
738	Me	Me	A1	COOH	CH ₂ CH ₂ O	J3	0	CH
739	Me	Me	A1	COOH	CH ₂ CH ₂ O	J4	0	CH
740	Me	Me	A1	COOH	CH ₂ CH ₂ O	J5	0	CH
741	Me	Me	A1	COOH	CH ₂ CH ₂ O	J6	0	CH
742	Me	Me	A1	COOH	CH ₂ CH ₂ O	J7	0	CH
743	Me	Me	A1	COOH	CH ₂ CH ₂ O	J8	0	CH
744	Me	Me	A1	COOH	CH ₂ CH ₂ O	J9	0	CH
745	Me	Me	A1	COOH	CH ₂ CH ₂ O	J10	0	CH
746	Me	Me	A1	COOH	CH ₂ CH ₂ O	J11	0	CH
747	Me	Me	A1	COOH	CH ₂ CH ₂ O	J12	0	CH
748	Me	Me	A1	COOH	CH ₂ CH ₂ O	J13	0	CH
749	Me	Me	A1	COOH	CH ₂ CH ₂ O	J14	0	CH

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Table 30 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
750	Me	Me	A1	COOH	CH ₂ CH ₂ O	J15	0	CH

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Table 31

Compound No.	R ¹	R ²	A	E	G	J	m	X
751	Me	Me	A1	COOH	CH ₂ CH ₂ O	J15	0	CH
752	Me	Me	A1	COOH	CH ₂ CH ₂ O	J16	0	CH
753	Me	Me	A1	COOH	CH ₂ CH ₂ O	J17	0	CH
754	Me	Me	A1	COOH	CH ₂ CH ₂ O	J18	0	CH
755	Me	Me	A1	COOH	CH ₂ CH ₂ O	J19	0	CH
756	Me	Me	A1	COOH	CH ₂ CH ₂ O	J20	0	CH
757	Me	Me	A1	COOH	CH ₂ CH ₂ O	J21	0	CH
758	Me	Me	A1	COOH	CH ₂ CH ₂ O	J22	0	CH
759	Me	Me	A1	COOH	CH ₂ CH ₂ O	J23	0	CH
760	Me	Me	A1	COOH	CH ₂ CH ₂ O	J24	0	CH
761	Me	Me	A1	COOH	CH ₂ CH ₂ O	J25	0	CH
762	Me	Me	A1	COOH	CH ₂ CH ₂ O	J26	0	CH
763	Me	Me	A1	COOH	CH ₂ CH ₂ O	J27	0	CH
764	Me	Me	A1	COOH	CH ₂ CH ₂ O	J28	0	CH
765	Me	Me	A1	COOH	CH ₂ CH ₂ O	J29	0	CH
766	Me	Me	A1	COOH	CH ₂ CH ₂ O	J30	0	CH
767	Me	Me	A1	COOH	CH ₂ CH ₂ O	J31	0	CH
768	Me	Me	A1	COOH	CH ₂ CH ₂ O	J32	0	CH
769	Me	Me	A1	COOH	CH ₂ CH ₂ O	J33	0	CH
770	Me	Me	A1	COOH	CH ₂ CH ₂ O	J34	0	CH
771	Me	Me	A1	COOH	CH ₂ CH ₂ O	J35	0	CH
772	Me	Me	A1	COOH	CH ₂ CH ₂ O	J37	0	CH
773	Me	Me	A1	COOH	CH ₂ CH ₂ O	J39	0	CH
774	Me	Me	A1	COOH	CH ₂ CH ₂ O	J62	0	CH
775	Me	Me	A1	COOH	CH ₂ CH ₂ O	J63	0	CH

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Table 32

Compound No.	R ¹	R ²	A	E	G	J	m	X
776	H	H	A1	COOH	CH ₂ S	J1	0	CH
777	H	H	A1	COOH	CH ₂ S	J2	0	CH
778	H	H	A1	COOH	CH ₂ S	J3	0	CH

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Table 32 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	779	H	H	A1	COOH	CH ₂ S	J4	0	CH
	780	H	H	A1	COOH	CH ₂ S	J8	0	CH
	781	H	H	A1	COOH	CH ₂ S	J9	0	CH
	782	H	H	A1	COOH	CH ₂ S	J10	0	CH
10	783	Me	Me	A1	COOH	CH ₂ S	J1	0	CH
	784	Me	Me	A1	COOH	CH ₂ S	J2	0	CH
	785	Me	Me	A1	COOH	CH ₂ S	J3	0	CH
	786	Me	Me	A1	COOH	CH ₂ S	J4	0	CH
15	787	Me	Me	A1	COOH	CH ₂ S	J8	0	CH
	788	Me	Me	A1	COOH	CH ₂ S	J9	0	CH
	789	Me	Me	A1	COOH	CH ₂ S	J10	0	CH
	790	H	H	A1	COOH	CH ₂ SO ₂	J1	0	CH
20	791	H	H	A1	COOH	CH ₂ SO ₂	J2	0	CH
	792	H	H	A1	COOH	CH ₂ SO ₂	J3	0	CH
	793	H	H	A1	COOH	CH ₂ SO ₂	J4	0	CH
	794	H	H	A1	COOH	CH ₂ SO ₂	J8	0	CH
25	795	H	H	A1	COOH	CH ₂ SO ₂	J9	0	CH
	796	H	H	A1	COOH	CH ₂ SO ₂	J10	0	CH
	797	Me	Me	A1	COOH	CH ₂ SO ₂	J1	0	CH
	798	Me	Me	A1	COOH	CH ₂ SO ₂	J2	0	CH
30	799	Me	Me	A1	COOH	CH ₂ SO ₂	J3	0	CH
	800	Me	Me	A1	COOH	CH ₂ SO ₂	J4	0	CH

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Table 33

	Compound No.	R ¹	R ²	A	E	G	J	m	X
40	801	Me	Me	A1	COOH	CH ₂ SO ₂	J8	0	CH
	802	Me	Me	A1	COOH	CH ₂ SO ₂	J9	0	CH
	803	Me	Me	A1	COOH	CH ₂ SO ₂	J10	0	CH
	804	Me	Me	A1	COOH	CH ₂	J81	0	CH
45	805	Me	Me	A1	COOH	CH ₂	J82	0	CH
	806	Me	Me	A1	COOH	CH ₂	J83	0	CH
	807	Me	Me	A1	COOH	CH ₂	J84	0	CH
	808	Me	Me	A1	COOH	CH ₂	J85	0	CH
50	809	H	H	A1	COOH	CH ₂	J81	0	CH
	810	H	H	A1	COOH	CH ₂	J82	0	CH
	811	H	H	A1	COOH	CH ₂	J83	0	CH

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Table 33 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	812	H	H	A1	COOH	CH ₂	J84	0	CH
	813	H	H	A1	COOH	CH ₂	J85	0	CH
	814	Me	Me	A1	COOH	CH ₂ CH ₂	J1	1	CH
	815	Me	Me	A1	COOH	CH ₂	J1	1	CH
	816	Me	Me	A1	COOH	CH ₂	J37	1	CH
10	817	Me	Me	A1	COOH	CH ₂	J39	1	CH
	818	Me	Me	A1	COOH	CH ₂	J50	1	CH
	819	Me	Me	A1	COOH	CH ₂	J63	1	CH
	820	Me	Me	A1	COOH	CH ₂	J64	1	CH
	821	Me	Me	A1	COOH	CH ₂	J65	1	CH
15	822	H	H	A1	COOH	CH ₂	J37	1	CH
	823	H	H	A1	COOH	CH ₂	J39	1	CH
	824	H	H	A1	COOH	CH ₂	J50	1	CH
	825	H	H	A1	COOH	CH ₂	J63	1	CH

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Table 34

	Compound No.	R ¹	R ²	A	E	G	J	m	X
30	826	H	H	A1	COOH	CH ₂	J64	1	CH
	827	H	H	A1	COOH	CH ₂	J65	1	CH
	828	Cl	Cl	A1	COOH	CH ₂	J37	1	CH
	829	Cl	Cl	A1	COOH	CH ₂	J39	1	CH
	830	Cl	Cl	A1	COOH	CH ₂	J50	1	CH
35	831	Cl	Cl	A1	COOH	CH ₂	J63	1	CH
	832	Cl	Cl	A1	COOH	CH ₂	J64	1	CH
	833	Cl	Cl	A1	COOH	CH ₂	J65	1	CH
	834	H	H	A4	COOH	CH ₂	J37	1	CH
	835	H	H	A4	COOH	CH ₂	J39	1	CH
40	836	H	H	A4	COOH	CH ₂	J50	1	CH
	837	H	H	A4	COOH	CH ₂	J63	1	CH
	838	H	H	A4	COOH	CH ₂	J64	1	CH
	839	H	H	A4	COOH	CH ₂	J65	1	CH
	840	H	H	A11	COOH	CH ₂	J37	1	CH
45	841	H	H	A11	COOH	CH ₂	J39	1	CH
	842	H	H	A11	COOH	CH ₂	J50	1	CH
	843	H	H	A11	COOH	CH ₂	J63	1	CH
	844	H	H	A11	COOH	CH ₂	J64	1	CH
	845	H	H	A11	COOH	CH ₂	J65	1	CH

Table 34 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
846	H	H	A18	COOH	CH ₂	J37	1	CH
847	H	H	A18	COOH	CH ₂	J39	1	CH
848	H	H	A18	COOH	CH ₂	J50	1	CH
849	H	H	A18	COOH	CH ₂	J63	1	CH
850	H	H	A18	COOH	CH ₂	J64	1	CH

Table 35

Compound No.	R ¹	R ²	A	E	G	J	m	X
851	H	H	A18	COOH	CH ₂	J65	1	CH
852	H	H	A20	COOH	CH ₂	J37	1	CH
853	H	H	A20	COOH	CH ₂	J39	1	CH
854	H	H	A20	COOH	CH ₂	J50	1	CH
855	H	H	A20	COOH	CH ₂	J63	1	CH
856	H	H	A20	COOH	CH ₂	J64	1	CH
857	H	H	A20	COOH	CH ₂	J65	1	CH
858	Me	Me	A1	COOH	CH ₂ CH ₂	J1	2	CH
859	Me	Me	A1	COOH	CH ₂	J1	2	CH
860	Me	Me	A1	COOH	CH ₂	J37	2	CH
861	Me	Me	A1	COOH	CH ₂	J39	2	CH
862	Me	Me	A1	COOH	CH ₂	J50	2	CH
863	Me	Me	A1	COOH	CH ₂	J63	2	CH
864	Me	Me	A1	COOH	CH ₂	J64	2	CH
865	Me	Me	A1	COOH	CH ₂	J65	2	CH
866	H	H	A1	COOH	CH ₂	J37	2	CH
867	H	H	A1	COOH	CH ₂	J39	2	CH
868	H	H	A1	COOH	CH ₂	J50	2	CH
869	H	H	A1	COOH	CH ₂	J63	2	CH
870	H	H	A1	COOH	CH ₂	J64	2	CH
871	H	H	A1	COOH	CH ₂	J65	2	CH
872	Cl	Cl	A1	COOH	CH ₂	J37	2	CH
873	Cl	Cl	A1	COOH	CH ₂	J39	2	CH
874	Cl	Cl	A1	COOH	CH ₂	J50	2	CH
875	Cl	Cl	A1	COOH	CH ₂	J63	2	CH

Table 36

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	876	Cl	Cl	A1	COOH	CH ₂	J64	2	CH
	877	Cl	Cl	A1	COOH	CH ₂	J65	2	CH
10	878	H	H	A1	COOH	CH ₂	J37	2	N
	879	H	H	A1	COOH	CH ₂	J39	2	N
	880	H	H	A1	COOH	CH ₂	J50	2	N
15	881	H	H	A1	COOH	CH ₂	J63	2	N
	882	H	H	A1	COOH	CH ₂	J64	2	N
	883	H	H	A1	COOH	CH ₂	J65	2	N
20	884	Me	H	A1	COOH	CH ₂	J37	2	CH
	885	Me	H	A1	COOH	CH ₂	J63	2	CH
	886	Me	H	A1	COOH	CH ₂	J64	2	CH
25	887	Me	H	A1	COOH	CH ₂	J65	2	CH
	888	H	H	A4	COOH	CH ₂	J37	2	CH
	889	H	H	A4	COOH	CH ₂	J63	2	CH
30	890	H	H	A4	COOH	CH ₂	J64	2	CH
	891	H	H	A4	COOH	CH ₂	J65	2	CH
	892	Me	Me	A4	COOH	CH ₂	J37	2	CH
35	893	Me	Me	A4	COOH	CH ₂	J63	2	CH
	894	Me	Me	A4	COOH	CH ₂	J64	2	CH
	895	Me	Me	A4	COOH	CH ₂	J65	2	CH
40	896	Cl	Cl	A4	COOH	CH ₂	J37	2	CH
	897	Cl	Cl	A4	COOH	CH ₂	J63	2	CH
	898	Cl	Cl	A4	COOH	CH ₂	J64	2	CH
	899	Cl	Cl	A4	COOH	CH ₂	J65	2	CH
45	900	H	H	A4	COOH	CH ₂	J37	2	N

Table 37

	Compound No.	R ¹	R ²	A	E	G	J	m	X
50	901	H	H	A4	COOH	CH ₂	J63	2	N
	902	H	H	A4	COOH	CH ₂	J64	2	N
55	903	H	H	A4	COOH	CH ₂	J65	2	N
	904	H	H	A11	COOH	CH ₂	J37	2	CH
	905	H	H	A11	COOH	CH ₂	J63	2	CH
	906	H	H	A11	COOH	CH ₂	J64	2	CH
	907	H	H	A11	COOH	CH ₂	J65	2	CH

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Table 37 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
908	Me	Me	A11	COOH	CH ₂	J37	2	CH
909	Me	Me	A11	COOH	CH ₂	J63	2	CH
910	Me	Me	A11	COOH	CH ₂	J64	2	CH
911	Me	Me	A11	COOH	CH ₂	J65	2	CH
912	Cl	Cl	A11	COOH	CH ₂	J37	2	CH
913	Cl	Cl	A11	COOH	CH ₂	J63	2	CH
914	Cl	Cl	A11	COOH	CH ₂	J64	2	CH
915	Cl	Cl	A11	COOH	CH ₂	J65	2	CH
916	H	H	A11	COOH	CH ₂	J37	2	N
917	H	H	A11	COOH	CH ₂	J63	2	N
918	H	H	A11	COOH	CH ₂	J64	2	N
919	H	H	A11	COOH	CH ₂	J65	2	N
920	Me	Me	A18	COOH	CH ₂	J37	2	CH
921	Me	Me	A18	COOH	CH ₂	J63	2	CH
922	Me	Me	A18	COOH	CH ₂	J64	2	CH
923	Me	Me	A18	COOH	CH ₂	J65	2	CH
924	H	H	A18	COOH	CH ₂	J37	2	CH
925	H	H	A18	COOH	CH ₂	J63	2	CH

30

Table 38

Compound No.	R ¹	R ²	A	E	G	J	m	X
926	H	H	A18	COOH	CH ₂	J64	2	CH
927	H	H	A18	COOH	CH ₂	J65	2	CH
928	Cl	Cl	A18	COOH	CH ₂	J37	2	CH
929	Cl	Cl	A18	COOH	CH ₂	J63	2	CH
930	Cl	Cl	A18	COOH	CH ₂	J64	2	CH
931	Cl	Cl	A18	COOH	CH ₂	J65	2	CH
932	H	H	A18	COOH	CH ₂	J37	2	N
933	H	H	A18	COOH	CH ₂	J63	2	N
934	H	H	A18	COOH	CH ₂	J64	2	N
935	H	H	A18	COOH	CH ₂	J65	2	N
936	Me	Me	A20	COOH	CH ₂	J37	2	CH
937	Me	Me	A20	COOH	CH ₂	J63	2	CH
938	Me	Me	A20	COOH	CH ₂	J64	2	CH
939	Me	Me	A20	COOH	CH ₂	J65	2	CH
940	H	H	A20	COOH	CH ₂	J37	2	CH

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Table 38 (continued)

	Compound No.	R ¹	R ²	A	E	G	J	m	X
5	941	H	H	A20	COOH	CH ₂	J63	2	CH
	942	H	H	A20	COOH	CH ₂	J64	2	CH
	943	H	H	A20	COOH	CH ₂	J65	2	CH
10	944	Cl	Cl	A20	COOH	CH ₂	J37	2	CH
	945	Cl	Cl	A20	COOH	CH ₂	J63	2	CH
	946	Cl	Cl	A20	COOH	CH ₂	J64	2	CH
15	947	Cl	Cl	A20	COOH	CH ₂	J65	2	CH
	948	H	H	A20	COOH	CH ₂	J37	2	N
	949	H	H	A20	COOH	CH ₂	J63	2	N
20	950	H	H	A20	COOH	CH ₂	J64	2	N

Table 39

	Compound No.	R ¹	R ²	A	E	G	J	m	X
25	951	H	H	A20	COOH	CH ₂	J65	2	N
	952	Me	Me	A1	tetrazol	CH ₂	J37	0	CH
	953	Me	Me	A1	tetrazol	CH ₂	J63	0	CH
30	954	Me	Me	A1	tetrazol	CH ₂	J64	0	CH
	955	Me	Me	A1	tetrazol	CH ₂	J65	0	CH
	956	H	H	A1	tetrazol	CH ₂	J37	0	CH
35	957	H	H	A1	tetrazol	CH ₂	J63	0	CH
	958	H	H	A1	tetrazol	CH ₂	J64	0	CH
	959	H	H	A1	tetrazol	CH ₂	J65	0	CH
40	960	Cl	Cl	A1	tetrazol	CH ₂	J37	0	CH
	961	Cl	Cl	A1	tetrazol	CH ₂	J63	0	CH
	962	Cl	Cl	A1	tetrazol	CH ₂	J64	0	CH
45	963	Cl	Cl	A1	tetrazol	CH ₂	J65	0	CH
	964	H	H	A1	tetrazol	CH ₂	J37	0	N
	965	H	H	A1	tetrazol	CH ₂	J63	0	N
50	966	H	H	A1	tetrazol	CH ₂	J64	0	N
	967	H	H	A1	tetrazol	CH ₂	J65	0	N
	968	H	H	A4	tetrazol	CH ₂	J37	0	CH
55	969	H	H	A4	tetrazol	CH ₂	J63	0	CH
	970	H	H	A4	tetrazol	CH ₂	J64	0	CH
	971	H	H	A4	tetrazol	CH ₂	J65	0	CH
55	972	H	H	A18	tetrazol	CH ₂	J37	0	CH
	973	H	H	A18	tetrazol	CH ₂	J63	0	CH
55	974	H	H	A18	tetrazol	CH ₂	J64	0	CH

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Table 39 (continued)

Compound No.	R ¹	R ²	A	E	G	J	m	X
975	H	H	A18	tetrazol	CH ₂	J65	0	CH

5

Table 40

Compound No.	R ¹	R ²	A	E	G	J	m	X
976	Me	Me	A19	tetrazol	CH ₂	J37	0	CH
977	Me	Me	A19	tetrazol	CH ₂	J63	0	CH
978	Me	Me	A19	tetrazol	CH ₂	J64	0	CH
979	Me	Me	A19	tetrazol	CH ₂	J65	0	CH
980	H	H	A19	tetrazol	CH ₂	J37	0	CH
981	H	H	A19	tetrazol	CH ₂	J63	0	CH
982	H	H	A19	tetrazol	CH ₂	J64	0	CH
983	H	H	A19	tetrazol	CH ₂	J65	0	CH
984	Me	Me	A20	tetrazol	CH ₂	J37	0	CH
985	Me	Me	A20	tetrazol	CH ₂	J63	0	CH
986	Me	Me	A20	tetrazol	CH ₂	J64	0	CH
987	Me	Me	A20	tetrazol	CH ₂	J65	0	CH
988	H	H	A20	tetrazol	CH ₂	J37	0	CH
989	H	H	A20	tetrazol	CH ₂	J63	0	CH
990	H	H	A20	tetrazol	CH ₂	J64	0	CH
991	H	H	A20	tetrazol	CH ₂	J65	0	CH

35

[0021] The thiobenzimidazole derivative (1) of the present invention in which E is COOH and m is 0 can be prepared by the synthetic method (A) or (B) shown below:

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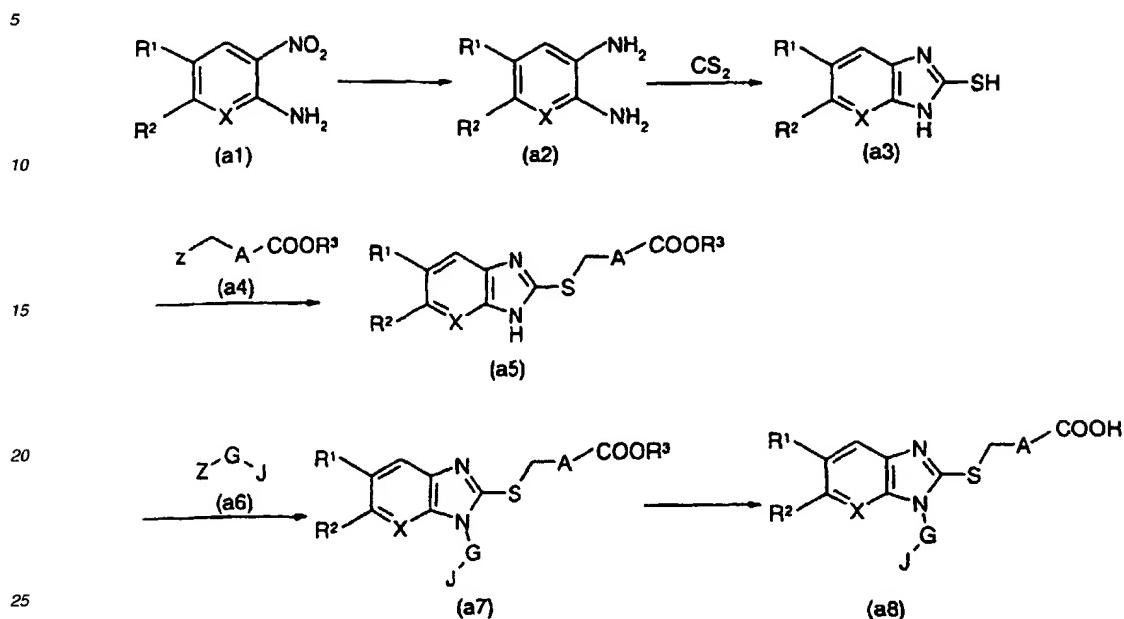
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Synthetic method (A)

[0022]



wherein Z represents a halogen, R¹, R², R³, A, G, J, and X are as defined above.

[0023] Thus, the nitro group of a 2-nitroaniline derivative (a1) is reduced to give an orthophenylenediamine (a2).

30 CS₂ is reacted with this diamine to produce a compound (a3), with which a halide ester derivative (a4) is reacted to obtain (a5). A halide derivative (a6) is reacted therewith to obtain (a7), which is hydrolyzed to yield a benzimidazole derivative (a8) of the present invention.

[0024] The reduction of the nitro group may be carried out under a standard condition for catalytic reduction. For example, a reaction is carried out with hydrogen gas in the presence of a catalyst such as Pd-C at a temperature of room temperature to 100°C. Alternatively, a method of treatment using zinc or tin under an acidic condition, or a method of using zinc powder at a neutral or alkaline condition can be used.

[0025] The reaction of an orthophenylenediamine derivative (a2) with CS₂ may be carried out using, for example, a method as described in J. Org. Chem. 19: 631-637, 1954, or J. Med. Chem. 36: 1175-1187, 1993 (EtOH solution).

[0026] The reaction of a thiobenzimidazole (a3) and a halide ester (a4) may be carried out according to the condition of the conventional S-alkylation, for example in the presence of a base such as NaH, Et₃N, NaOH, or K₂CO₃ at a temperature of 0°C to 200°C under stirring.

[0027] The reaction of a thiobenzimidazole (a5) and a halide derivative (a6) may be carried out according to the condition for the conventional N-alkylation or N-acylation, for example in the presence of a base such as NaH, Et₃N, NaOH, or K₂CO₃ at a temperature of 0°C to 200°C under stirring.

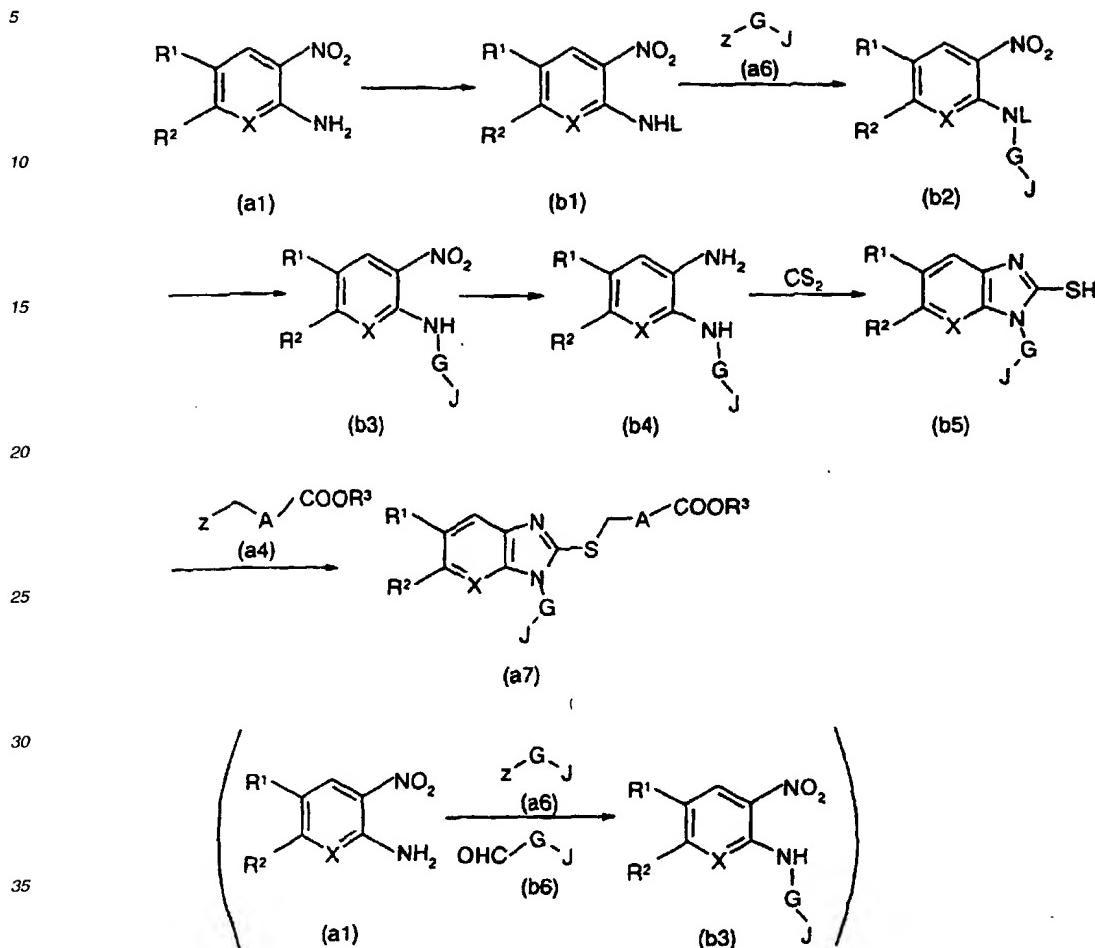
45 [0028] As the elimination reaction of the carboxy protecting group R³, preferably a method of hydrolysis is employed using an alkali such as lithium hydroxide or an acid such as trifluoroacetic acid.

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Synthetic method (B)

[0029]

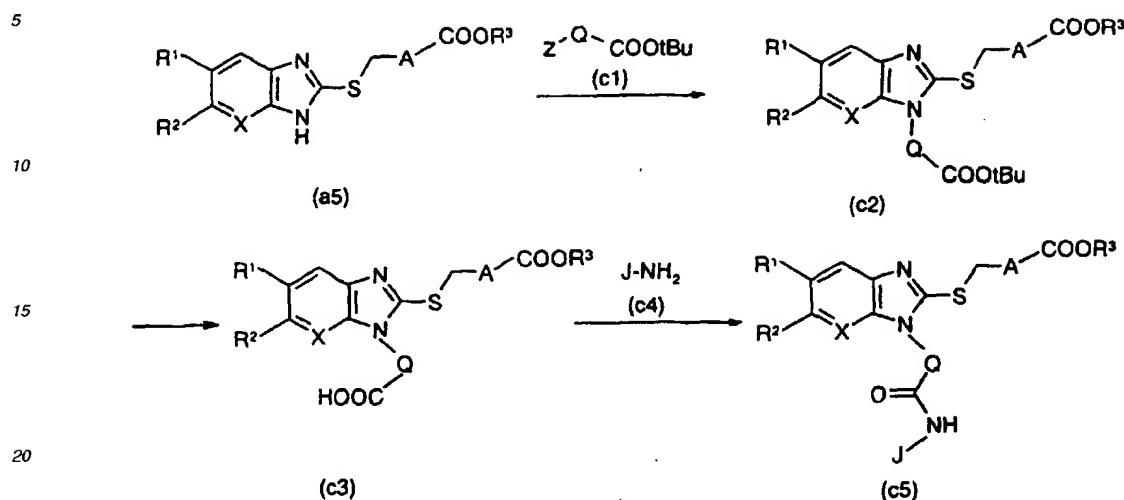


[0030] Thus, the amino group of a 2-nitroaniline derivative (a1) can be protected with L to give (b1). A halide derivative (a6) is reacted therewith to obtain (b2), from which L is deprotected to obtain (b3). The nitro group of (b3) is reduced to obtain an orthophenylene diamine derivative (b4). CS₂ is reacted therewith to yield a compound (b5), with which a halide ester derivative (a4) is reacted to obtain (a7) which may be hydrolyzed to yield a benzimidazole derivative of the present invention. Alternatively, it is also possible to obtain a compound (b3) directly by allowing the 2-nitroaniline derivative (a1) as it is unprotected to be reacted to a halide derivative (a6) or an aldehyde derivative (b6). As the protecting group L, there can be mentioned a trifluoroacetic acetyl group, an acetyl group, a t-butoxycarbonyl group, a benzyl group, and the like. The reaction of the 2-nitroaniline derivative (a1) and the aldehyde derivative (b6) may be carried out according to the conditions of the conventional reductive amination using a reducing agent such as a complex hydrogen compound, for example LiAlH₄, NaBH₄, NaB₃CN, NaBH(OAc)₃, etc. or borane, in a solvent such as ethanol, methanol, and dichloromethane at a temperature condition of 0°C to 200°C. The other reactions may be carried out as in the Synthetic method (A).

[0031] The thiobenzimidazole derivative (1) of the present invention in which E is COOH, m is 0, and G is an amide bond can be prepared by the synthetic method (C) shown below:

Synthetic method (C)

[0032]



wherein Q represents a methylene group, a phenylene group, etc., and Z represents a halogen. R¹, R², R³, A, J, 25 and X are as defined above, provided that R³ is a protecting group such as an ethyl group, a methyl group, etc. inactive in an acid.

[0033] Thus, a tert-butyl ester halide derivative (c1) is reacted with a thiobenzimidazole compound (a5) to obtain a 30 compound (c2), which is subjected to hydrolysis under an acidic condition to yield (c3). An amine derivative (c4) is reacted therewith to yield (c5), which is subjected to hydrolysis to obtain the benzimidazole derivative of the present invention.

[0034] The condensation amidation may be carried out by a conventional method using a condensing agent. As the 35 condensing agent, there can be mentioned DCC, DIPC, EDC=WSCl, WSCl • HCl, BOP, DPPA, etc., which may be used alone or in combination with HONSu, HOEt, HOObt, etc. The reaction may be carried out in an appropriate solvent such as THF, chloroform, t-butanol, etc. at a temperature condition of 0°C to 200°C. The other reactions may be carried out as in the Synthetic method (A).

[0035] The thiobenzimidazole derivative (1) of the present invention in which E is COOH, m is 0, and G is an ether bond can be prepared by the synthetic method (D) shown below:

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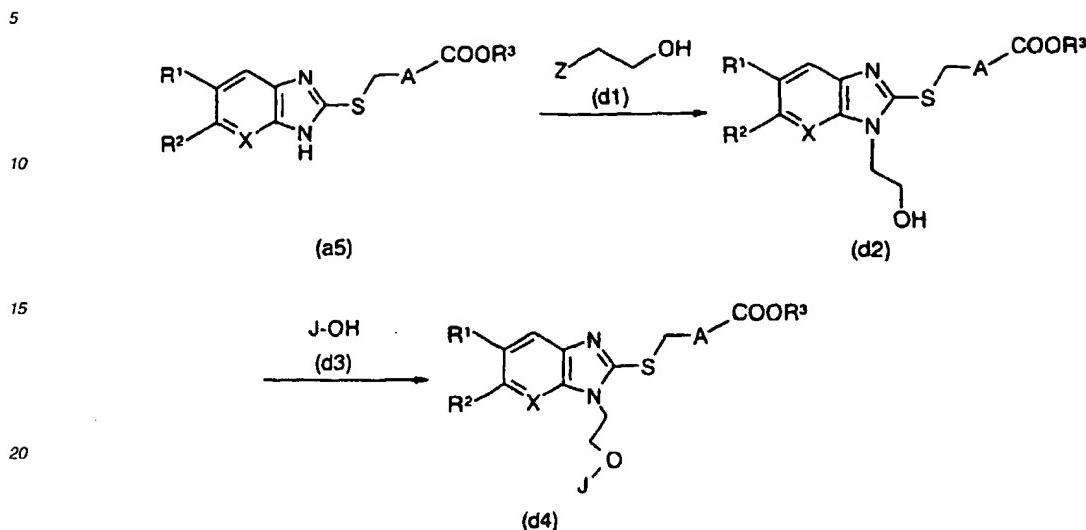
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Synthetic method (D)

[0036]



25 wherein Z represents a halogen, R¹, R², R³, A, J, and X are as defined above.

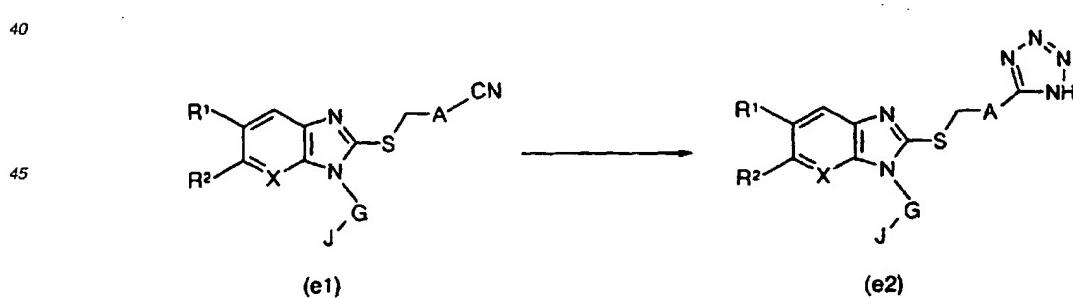
[0037] Thus, a thiobenzimidazole compound (a5) is reacted with, for example, a halide alcohol derivative (d1) to yield a compound (d2). A phenol derivative (d3) is reacted therewith to yield an ether (d4), which is subjected to hydrolysis to yield a benzimidazole derivative (a8) of the present invention.

[0038] The etherification may be carried out using a phosphine compound such as triphenyl phosphine and tributyl phosphine and an azo compound such as DEAD and TMAD in a suitable solvent such as N-methylmorpholine and THF at a temperature of 0°C to 200°C in a Mitsunobu reaction or a related reaction thereof. The other reactions may be carried out as in the Synthetic method (A).

[0039] The thiobenzimidazole derivative (1) of the present invention in which E is a tetrazole and m is 0 can be prepared by the synthetic method (E) shown below:

35 Synthetic method (E)

[0040]



wherein R¹, R², A, G, J, and X are as defined above.

[0041] A nitrile (e1) is reacted with various azi compounds to be converted to a tetrazole (e2).

[0042] As the azi compound, there can be mentioned a trialkyltin azide compound such as trimethyltin azide, and hydrazoic acid or an ammonium salt thereof. When an organic tin azide compound is used, 1-4 fold molar amount is used relative to the compound (e1). When hydrazoic acid or an ammonium salt thereof is used, 1-5 fold molar amount of sodium azide or a tertiary amine such as ammonium chloride and triethylamine may be used relative to the com-

pound (e1). Each reaction may be carried out at a temperature of 0°C to 200°C in a solvent such as toluene, benzene and DMF.

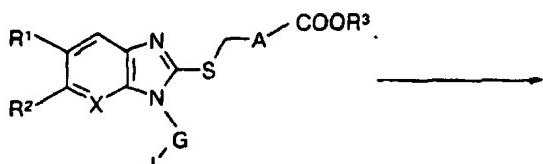
[0043] The thiobenzimidazole derivative (1) of the present invention in which m is 1 or 2 can be prepared by the synthetic method (F) shown below:

5

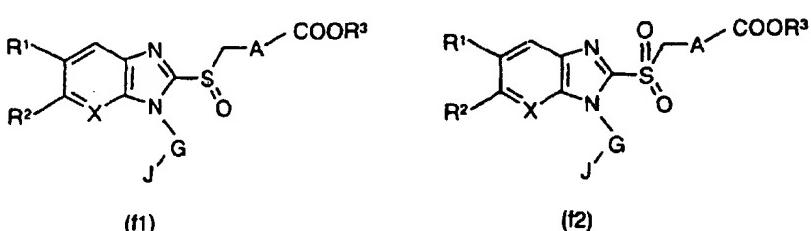
Synthetic method (F)

[0044]

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15



25

wherein R¹, R², R³, A, G, J, and X are as defined above.

30 [0045] Thus, a thiobenzimidazole compound (a7) may be reacted with a peroxide compound in a suitable medium to yield a sulfoxide derivative (f1) and/or a sulfone derivative (f2). As the peroxide compound used, there can be mentioned perbenzoic acid, m-chloroperbenzoic acid, peracetic acid, hydrogen peroxide, and the like, and as the solvent used, there can be mentioned chloroform, dichloromethane, and the like. The ratio of the compound (a7) to the peroxide compound used is selected from, but not limited to, a broad range as appropriate, and generally 1.2 to 5 fold molar amount, for example, may be preferably used. Each reaction is carried out generally at about 0 to 50°C, and preferably at 0°C to room temperature, and is generally complete in about 4-20 hours.

35 [0046] The benzimidazole derivatives of the present invention can be converted, as needed, to medically acceptable non-toxic cation salts. As such a salt, there can be mentioned an alkali metal ion such as Na⁺ and K⁺; an alkaline earth metal ion such as Mg²⁺ and Ca²⁺; a metal ion such as Al³⁺ and Zn²⁺; or an organic base such as ammonia, triethylamine, ethylenediamine, propanediamine, pyrrolidine, piperidine, piperadine, pyridine, lysine, choline, ethanolamine, N,N-diethylethanolamine, 4-hydroxypiperidine, glucosamine, and N-methylglucamine. Among them, Na⁺, Ca²⁺, lysine, choline, N,N-dimethylethanolamine and N-methylglucamine are preferred.

40 [0047] The benzimidazole derivatives of the present invention inhibit human chymase activity. Specifically, their IC₅₀ is not greater than 1000, preferably not smaller than 0.01 and less than 1000, and more preferably not smaller than 0.05 and less than 500. The benzimidazole derivatives of the present invention having such excellent inhibitory action on human chymase can be used as clinically applicable preventive and/or therapeutic agents for various diseases.

45 [0048] The benzimidazole derivatives of the present invention can be administered as pharmaceutical compositions together with pharmaceutically acceptable carriers by oral or parenteral routes after being shaped into various dosage forms. As the parenteral administration, there can be mentioned intravenous, subcutaneous, intramuscular, percutaneous, rectal, nasal, and eye drop administration.

50 [0049] Dosage forms for said pharmaceutical compositions include the following. For example, in the case of oral administration, there can be mentioned dosage forms such as tablets, pills, granules, powders, solutions, suspensions, syrups, and capsules.

55 [0050] As used herein, tablets are shaped by a conventional method using a pharmaceutically acceptable carrier such as an excipient, a binder, and a disintegrant. Pills, granules, and powders can also be shaped by a conventional method using an excipient etc. Solutions, suspensions, and syrups may be shaped by a conventional method using glycerin esters, alcohols, water, vegetable oils, and the like. Capsules can be shaped by filling a granule, a powder, and a solution into a capsule made of gelatin etc.

[0051] Among the parenteral preparations, those for intravenous, subcutaneous, and intramuscular administration can be administered as an injection. As injections, a benzoic acid derivative is dissolved in a water soluble liquid such as physiological saline, or in a non-water soluble liquid comprising an organic ester such as propylene glycol, polyethylene glycol, and a vegetable oil.

5 [0052] In the case of percutaneous administration, dosage forms such as ointments and creams can be used. Ointments can be prepared by mixing a benzoic acid derivative with a fat or lipid, vaseline, etc., and creams can be prepared by mixing a benzoic acid derivative with an emulsifier.

[0053] In the case of rectal administration, gelatin soft capsules can be used to prepare suppositories.

10 [0054] In the case of nasal administration, they can be used as a formulation comprising a liquid or powder composition. As the base for liquid formulations, water, saline, a phosphate buffer, an acetate buffer etc. can be used, and furthermore they may include a surfactant, an antioxidant, a stabilizer, a preservative, and a thickening agent. As the base for powder formulations, there can be mentioned polyacrylic acid salts that are readily solubile in water, cellulose lower alkyl ethers, polyethylene glycol, polyvinylpyrrolidone, amylose, pullulan, etc. that are water-absorptive, or celluloses, starches, proteins, gums, crosslinked vinyl polymers, etc. that are hardly water-soluble, and preferably they are water-absorptive. Alternatively, they may be combined. Furthermore, for powder formulations, an antioxidant, a colorant, a preservative, a disinfectant, a corrigent, etc. can be added. Such liquid formulations and powder formulations can be administered using, for example, a spraying device etc.

15 [0055] For eye drop administration, they can be used as aqueous or non-aqueous eye drops. For the aqueous eye drops, sterile purified water, physiological saline etc. can be used as a solvent. When sterile purified water is used as the solvent, a suspending agent such as a surfactant and a polymer thickener may be added to prepare an aqueous eye drop suspension. Alternatively, a solubilizing agent such as a nonionic surfactant may be added to prepare a soluble eye drop solution. The non-aqueous eye drop can use a non-aqueous solvent for injection as a solvent, and can be used as a non-aqueous eye drop solution.

20 [0056] In the case where administration to the eye is performed by a method other than the eye drop, dosage forms such as an eye ointment, an application solution, an epipastic, and an insert can be used.

25 [0057] In the case of nasal or oral inhalation, they are inhaled as a solution or a suspension of the benzimidazole derivatives of the present invention with a commonly used pharmaceutical excipient using, for example, an aerosol spray for inhalation, etc. Alternatively, the benzimidazole derivatives of the present invention in a lyophilized powder form can be administered to the lung using an inhaling device that permits direct contact to the lung.

30 [0058] To such various formulations, pharmaceutically acceptable carriers such as an isotonic agent, a preservative, a disinfectant, a wetting agent, a buffering agent, an emulsifier, a dispersant, a stabilizer, etc. can be added as needed.

35 [0059] To these formulations, blending of an antimicrobial agent, a treatment such as filtration through a bacteria-retaining filter, heating, radiation, etc. can be carried out for sterilization. Alternatively, sterile solid formulations can be prepared, which may be used by dissolving or suspending them in an appropriate sterile solution immediately prior to use.

40 [0060] The dosages of the benzimidazole derivatives of the present invention vary depending on the type of diseases, route of administration, the condition, age, sex, body weight etc. of the patient, but they are generally in the range of about 1 to 500 mg/day/patient for oral administration, and preferably 1 to 300 mg/day/patient. In the case of parenteral administration such as intravenous, subcutaneous, intramuscular, percutaneous, rectal, nasal, eye drop, and inhalation administration, they are about 0.1 to 100 mg/day/patient, and preferably 0.3 to 30 mg/day/patient.

45 [0061] When the benzimidazole derivatives of the present invention are used as a preventive agent, they can be administered according to a known method depending on each condition.

[0062] As the target diseases for the preventive and/or therapeutic agents of the present invention, there can be mentioned, for example, diseases of respiratory organs such as bronchial asthma, inflammatory/allergic diseases such as allergic rhinitis, atopic dermatitis, and urticaria; diseases of circulatory organs such as sclerosing vascular lesions, intravascular stenosis, disturbances of peripheral circulation, renal failure, and cardiac failure; diseases of bone/cartilage metabolism such as rheumatoid arthritis and osteoarthritis.

50 Examples

[0063] The present invention will now be explained in more detail with reference to Preparation Examples, Working Examples, and Test Examples. It should be noted, however, that these examples do not limit the scope of the invention in any way.

55 Reference Example 1. Preparation of 5,6-dimethylbenzimidazole-2-thiol

[0064] To 5,6-dimethylorthophenylene diamine (4.5 g, 33 mmol) in pyridine (40 ml) was added carbon disulfide (40

ml, 0.66 mol). The resulting solution was heated to reflux under stirring for 18 hours, to which was added water, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous magnesium sulfate, it was concentrated, and dried under reduced pressure at 80°C for 6 hours to obtain the title compound (4.1 g, yield 70%).

5 Reference Example 2. Preparation of 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester

[0065] To the resulting 5,6-dimethylbenzimidazole-2-thiol (89 mg, 0.50 mmol) in dimethylformamide (2 ml), triethylamine (84 µl, 0.6 mmol) and 2-bromomethyl benzoic acid methyl ester (137 mg, 0.6 mmol) were added. After the resulting solution was stirred at 80°C for 1.5 hours, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous magnesium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain the title compound (146 mg, yield 90%). The compound was confirmed by identification of molecular weight using LC-MS. Calculated M = 326.11, measured (M+H)⁺ = 327.2

15 Reference Example 3.

[0066] In a similar manner to Reference Example 2, the following compounds were synthesized. The compounds were confirmed by identification of molecular weight using LC-MS.

20 3-((5,6-dimethylbenzimidazole-2-ylthio)methyl)pyridine-2-carboxylic acid ethyl ester

[0067]

Calculated M = 341.12, found (M+H)⁺ = 342.2

25 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)furan-3-carboxylic acid methyl ester

[0068]

30 Calculated M = 316.09, found (M+H)⁺ = 317.2

3-((5,6-dimethylbenzimidazole-2-ylthio)methyl)thiophene-2-carboxylic acid methyl ester

[0069]

35 Calculated M = 332.07, found (M+H)⁺ = 333.2

2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester

40 [0070]

Calculated M = 298.08, found (M+H)⁺ = 299.2

3-(benzimidazole-2-ylthiomethyl)pyridine-2-carboxylic acid ethyl ester

45 [0071]

Calculated M = 313.09, found (M+H)⁺ = 314.2

50 3-(benzimidazole-2-ylthiomethyl)thiophene-2-carboxylic acid methyl ester

[0072]

Calculated M = 304.03, found (M+H)⁺ = 305.2

2-(benzimidazole-2-ylthiomethyl)furan-3-carboxylic acid methyl ester

[0073]

5 Calculated M = 288.06, found (M+H)⁺ = 289.24-benzimidazole-2-ylthiobutanoic acid methyl ester

[0074]

10 Calculated M = 264.09, found (M+H)⁺ = 265.22-((5,6-dichlorobenzimidazole-2-ylthio)methyl)-5-chlorobenzoic acid methyl ester

15 [0075]

Calculated M = 399.96, found (M+H)⁺ = 401.22-(benzimidazole-2-ylthiomethyl)-5-chlorobenzoic acid methyl ester

20 [0076]

Calculated M = 332.04, found (M+H)⁺ = 333.225 4-((5,6-dimethylbenzimidazole-2-ylthio)butanoic acid ethyl ester

[0077]

Calculated M = 292.12, found (M+H)⁺ = 293.4030 2-((5,6-dichlorobenzimidazole-2-ylthio)methyl)benzoic acid methyl ester

[0078]

35 Calculated M = 366.00, found (M+H)⁺ = 367.02-((5,6-dichlorobenzimidazole-2-ylthio)methyl)pyridine-3-carboxylic acid methyl ester

[0079]

40 Calculated M = 366.99, found (M+H)⁺ = 368.0Example 1 Preparation of compound No. 143

45 [0080] Sodium hydride (11 mg, 0.306 mmol) and 2 ml of tetrahydrofuran was added to a previously dried reaction vessel. To the mixture were added 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester (50 mg, 0.153 mmol) and 1-chloromethylnaphthalene (69 µl, 0.459 mmol), which was then stirred at 60°C for 45 minutes. Water was added thereto, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain 2-((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (yield 32%).

[0081] To 2-((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (23 mg, 0.08 mmol) in tetrahydrofuran (1 ml) and methanol (0.5 ml), 4N aqueous sodium hydroxide solution (0.25 ml) was added. After stirring at room temperature for 5 hours, 6N hydrochloric acid was added to stop the reaction, followed by extraction with ethyl acetate. The ethyl acetate phase was washed with saturated saline, and then dried in anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (24 mg, yield quantitative).

[0082] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 452.16, found (M+H)⁺ = 453.2

Example 2.

- 5 [0083] In a similar manner to Working Example 1, the compounds in Tables 41 to 45 were synthesized using the compounds in Reference Examples 2 or 3 and various halide derivatives. The compounds were confirmed by identification of molecular weight using LC-MS.

Table 41

Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
390	406.14	407.2	29
391	422.11	423.2	16
315	417.15	418.2	32
376	406.14	407.2	25
333	417.15	418.2	6
82	416.16	417.2	12
83	416.16	417.2	9
84	416.16	417.2	33
97	432.15	433.2	18
98	432.15	433.2	26
99	432.15	433.2	8
94	470.13	471.2	14
95	470.13	471.2	10
96	470.13	471.2	13
100	486.12	487.2	26
101	486.12	487.2	8
85	420.13	421.2	9
86	420.13	421.0	12
87	420.13	421.2	44
88	436.10	437.2	42
89	436.10	437.2	40
90	436.10	437.2	28
91	480.07	481.0	12
103	427.14	428.2	12
104	427.14	428.2	6
105	427.14	428.2	11
784	434.11	435.2	36

Table 42

	Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
5	787	468.07	469.2	31
10	112	418.14	419.2	40
15	141	480.12	481.0	72
20	138	494.17	495.2	34
25	135	446.13	447.2	19
30	137	478.17	479.2	6
35	143	452.16	453.2	35
40	142	452.16	453.0	30
45	139	428.16	429.4	22
50	140	458.20	459.2	5
55	63	424.12	425.2	25
60	311	453.15	454.5	21
65	115	430.17	431.5	68
70	116	430.17	431.5	52
75	117	430.17	431.5	41
80	118	430.17	431.5	56
85	125	462.16	463.0	59
90	126	462.16	463.0	25
95	128	492.17	493.0	27
100	134	446.13	447.0	34
105	108	446.17	447.0	75
110	107	446.17	447.0	57
115	119	470.06	471.0	36
120	120	470.06	471.0	57
125	121	470.06	471.0	60
130	122	470.06	471.0	37
135	123	430.17	431.3	57

Table 43

	Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
50	124	462.16	463.3	67
55	127	462.16	463.3	62
60	129	446.17	447.3	47
65	130	446.17	447.3	40
70	319	425.12	426.3	30

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Table 43 (continued)

	Compound No.	Calculated M	Found ($M+H$) ⁺	Recovery % (overall)
5	506	466.17	467.2	16
	505	466.17	467.0	14
	93	480.07	481.0	45
10	136	478.17	479.2	60
	37	402.14	403.4	25
	39	442.03	443.0	51
	317	403.14	404.0	56
	318	443.03	444.0	46
	380	442.14	443.2	51
15	377	420.15	421.2	34
	378	460.04	461.0	30
	386	414.10	415.2	37
	383	392.12	393.2	30
	384	432.01	433.0	29
20	395	458.11	459.2	23
	392	436.13	437.2	15
	393	476.02	477.0	15
	401	430.08	431.2	50
	398	408.10	409.2	20
30	399	447.99	449.0	7

35

Table 44

	Compound No.	Calculated M	Found ($M+H$) ⁺	Recovery % (overall)
40	544	476.13	377.2	62
	50	418.14	419.2	42
	459	382.08	383.2	65
45	402	436.04	437.2	50
	1	388.12	389.0	38
	161	456.05	457.0	54
	81	402.14	403.3	57
	154	444.13	445.0	32
50	160	408.10	409.0	72
	159	421.15	422.2	84
	148	482.17	483.5	64
	149	453.15	454.5	71
	155	459.11	460.0	64

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Table 44 (continued)

	Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
5	150	453.15	454.2	36
	151	487.11	488.1	62
	153	460.10	461.0	69
	152	454.15	455.0	62
10	64	430.08	431.2	85
	455	410.11	411.2	17
	596	430.14	431.2	56
	539	418.17	419.2	20
15	349	436.10	437.1	50
	352	458.09	459.2	74
	168	470.06	471.1	57
	355	504.02	505.0	26
20	174	492.05	493.0	89
	358	526.01	527.1	38

25

Table 45

	Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
30	324	493.04	494.2	32
	320	431.08	432.1	15
	147	466.17	467.2	72
35	616	490.16	491.2	22
	805	382.17	383.2	52
	804	368.16	369.2	56
	66	438.14	439.2	54
40	592	430.14	432.3	5
	811	380.16	382.2	72
	582	436.06	437.1	59
	580	436.06	437.1	59
45	584	480.03	483.1	37
	583	480.03	483.0	52
	578	420.09	421.2	30
	574	416.12	417.2	39
50	595	452.12	453.2	22
	594	478.14	479.1	23
	588	432.11	433.1	65
	587	432.11	433.2	48
55	586	432.11	433.1	50

Table 45 (continued)

Compound No.	Calculated M	Found (M+H) ⁺	Recovery % (overall)
590	427.10	428.2	24
589	427.10	428.3	17

Example 3. Preparation of compound No. 547

- 10 [0084] Triethylamine (276 µl, 1.98 mmol) and 2-(bromoethyl)benzoic acid t-butyl ester (538 mg, 1.99 mmol) were added to 5,6-dimethylbenzimidazole-2-thiol (236 mg, 1.32 mmol) in 2 ml of dimethylformamide, which was then stirred at 80°C for 3 hours. After the reaction was complete, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain 2-((5,6-dimethylbenzimidazole-2-ylothio)methyl)benzoic acid t-butyl ester (288 mg, yield 59%).
- 15 [0085] 2-((5,6-dimethylbenzimidazole-2-ylothio)methyl)benzoic acid t-butyl ester (30 mg, 0.082 mmol) was dissolved in 3 ml of chloroform, to which triethylamine (17 µl, 0.123 mmol) and benzoyl chloride (14 µl, 0.123 mmol) were sequentially added and the mixture was stirred at room temperature for 2 hours. After the reaction was complete, water was added, followed by extraction with ethyl acetate. After drying the ethyl acetate phase with anhydrous sodium sulfate, it was concentrated, and 2-((5,6-dimethyl-1-(phenylcarbonyl)benzimidazole-2-ylothio)methyl)benzoic acid t-butyl ester was obtained (38 mg, yield quantitative).
- 20 [0086] 2-((5,6-dimethyl-1-(phenylcarbonyl)benzimidazole-2-ylothio)methyl)benzoic acid t-butyl ester was dissolved in 1 ml of dichloromethane, to which trifluoroacetic acid (1 ml) was added and the mixture was stirred at room temperature for 6 hours. After the reaction was complete, the solvent was evaporated under reduced pressure and dried overnight to obtain the title compound (33 mg, yield quantitative).
- 25 [0087] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 416.12, found (M+H)⁺ = 417.0

Example 4. Preparation of compound No. 561

- [0088] The title compound was obtained in a similar manner to Working Example 3.
- [0089] The compound was confirmed by identification of molecular weight using LC-MS.

35 Calculated M = 452.09, found (M+H)⁺ = 453.2

Reference Example 4. Preparation of 3-(naphthylmethyl)imidazo[5,4-b]pyridine-2-thiol

- 40 [0090] To 2-amino-3-nitropyridine (1680 mg, 12 mmol) in a dimethylformamide (20 ml), sodium hydride (75 mg, 0.55 mmol) and 1-chloromethylnaphthalene (74 µl, 0.55 mmol) were added. After the resulting solution was stirred at 80°C for 17 hours, water was added thereto, followed by extraction with ethyl ether. After drying the ethyl ether phase with anhydrous magnesium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain of naphthylmethyl(3-nitro(2-pyridil))amine (903 mg, yield 27%).
- [0091] To naphthylmethyl(3-nitro(2-pyridil))amine (900 mg, 3.2 mmol) in ethanol (40 ml), 90.0 mg of 10% Pd-C was added. After the resulting solution was stirred in a hydrogen atmosphere at 50°C for 8 hours, it was filtered through celite to remove Pd-C. The resulting solution was concentrated to obtain (3-amino(2-pyridil))naphthylmethylamine (860 mg, yield 99%). To the resulting (3-amino(2-pyridil))naphthylmethylamine (860 mg, 3.2 mmol) in ethanol (20 ml), carbon disulfide (6.1 ml, 102 mmol) was added. After the resulting solution was heated to reflux under stirring for 12 hours, it was allowed to stand at room temperature for 5 hours. The precipitate that deposited was filtered, and was washed three times with ethanol (5 ml). It was dried at 80°C under reduced pressure for 5 hours to obtain the title compound (555 mg, yield 56%).
- [0092] The compound was confirmed by identification of molecular weight using LC-MS.

55 Calculated M = 291.08, found (M+H)⁺ = 292.3

Reference Example 5. Preparation of 3-((2,5-dimethylphenyl)methyl)imidazo[5,4-b]pyridine-2-thiol

- [0093] The title compound was synthesized in a similar manner to Reference Example 4.

[0094] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 269.01, found (M+H)⁺ = 270.2

5 Example 5. Preparation of compound No. 256

[0095] Using 3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-thiol (30 mg, 0.1 mmol) obtained in Reference Example 4 in a similar manner to Reference Example 2, 2-((3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-ylthio)methyl)benzoic acid methyl ester was obtained (30 mg, yield 70%).

10 [0096] The 2-((3-(naphthylmethyl)imidazolo(5,4-b)pyridine-2-thio)methyl)benzoic acid methyl ester (30 mg, 0.068 mmol) thus obtained was subjected to hydrolysis in a similar manner to Example 1 to obtain the title compound (18.3 mg, yield 66%).

[0097] The compound was confirmed by identification of molecular weight using LC-MS.

15 Calculated M = 425.12, found (M+H)⁺ = 426.1

Example 6.

20 [0098] The compounds in Table 46 were synthesized using the compounds obtained in Reference Examples 4 and 5 and various halide ester derivatives in a similar manner to Example 5.

[0099] The compounds were confirmed by identification of molecular weight using LC-MS.

Table 46

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
253	403.14	407.2	67
327	404.13	423.2	46
329	426.12	418.2	58
361	437.10	438.0	52
364	459.08	460.0	66

35

Table 47

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
321	428.13	429.2	27
354	461.10	462.2	20
460	379.14	380.2	19

45

Table 48

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
52	493.15	494.2	12
53	493.15	494.2	11

55

Example 7. Preparation of compound No. 264

[0100] 4-methyl-2-nitroaniline (913 mg, 6 mmol) was dissolved in acetonitrile (18 ml), to which anhydrous trifluoro-

acetic acid (1.00 ml, 7.2 mmol) was added and the mixture was subjected to reflux for 1.5 hours. After cooling to room temperature, it was concentrated under reduced pressure and dried to obtain 4-methyl-2-nitro trifluoroacetanilide (1.396 g, yield 94%).

[0101] 4-methyl-2-nitro trifluoroacetanilide (1.396 g, 5.63 mmol) was dissolved in dimethylformamide (14 ml), and then potassium carbonate (940 mg, 6.80 mmol) and 1-chloromethylnaphthalene (1.15 g, 6.51 mmol) were sequentially added at room temperature and heated to 100°C. After 1 hour and 40 minutes, 5N aqueous sodium hydroxide solution (7.5 ml) was added and refluxed as it was for 15 minutes. After 15 minutes, it was cooled to room temperature, and water (180 ml) was added and stored at 4°C overnight. The crystals that deposited were filtered and were dried to obtain ((1-naphthyl)methyl)(4-methyl-2-nitro-phenyl)amine (1.587 g, yield 96%).

[0102] To (1-naphthyl)methyl)(4-methyl-2-nitro-phenyl)amine (1.0021 g, 3.43 mmol), ethanol (5 ml) and 1,4-dioxane (5 ml) were added, and 2.058 M aqueous sodium hydroxide solution (1 ml) was further added, and refluxed in an oil bath. After 15 minutes, it was removed from the oil bath, and zinc powder (897 mg, 13.72 mmol) was fed thereto in portions. Then it was refluxed again in the oil bath for 2 hours. After 2 hours, it was concentrated under reduced pressure, and dissolved in ethyl acetate (50 ml), and washed twice with saturated saline (25 ml). After drying with magnesium sulfate, it was concentrated under reduced pressure and dried to obtain a brown oil of ((1-naphthyl)methyl)(2-amino-4-methyl-phenyl)amine (943.1 mg).

[0103] Subsequently, ((1-naphthyl)methyl)(2-amino-4-methyl-phenyl)amine (943.1 mg, 3.59 mmol) was dissolved in ethanol (6.4 ml), to which carbon bisulfide (7 ml, 116 mmol) was added, and then refluxed. After 10 hours, it was returned to room temperature, concentrated under reduced pressure. Ethanol (2 ml) was added to the residue, which was stirred at room temperature for 30 minutes, and was further stirred on ice for 30 minutes. The resulting crystals were filtered, and dried to obtain 1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-thiol (459.1 mg, yield 44%, 2 steps).

[0104] 1-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-thiol (431.1 mg, 1.42 mmol) was dissolved in dimethylformamide (12 ml), to which triethylamine (0.296 ml, 2.12 mmol) and 2-bromomethyl benzoic acid methyl ester (390.1 mg, 1.70 mmol) were added and heated to 80°C. After 5 hours and 50 minutes, triethylamine (0.296 ml, 2.12 mmol) and 2-bromomethyl benzoic acid methyl ester (325 mg, 1.42 mmol) were added, and heated for 1 hour and 10 minutes. Thereafter, it was concentrated under reduced pressure, and dissolved in ethyl acetate (80 ml), washed twice with water (30 ml), and dried in magnesium sulfate. The solvent was concentrated under reduced pressure. The residue was crystallized in ethyl acetate-hexane to obtain 410 mg, and the mother liquor was purified by silica gel column chromatography (hexane : ethyl acetate = 6:1) to recover 87 mg of the same fraction as the crystals, with a total of 497 mg of 2-((1-naphthyl)methyl)-6-methyl-benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (yield 78%).

[0105] 2-((1-(1-naphthyl)methyl)-6-methyl-benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (497 mg, 1.098 mmol) was dissolved in methanol (10 ml) and tetrahydrofuran (10 ml), to which 4N aqueous lithium hydroxide solution (6.86 ml) was added. After stirring at room temperature for 2 hours and 30 minutes, saturated aqueous citric acid solution (10 ml) was added thereto to stop the reaction, and the mixture was concentrated under reduced pressure to reduce the amount of the solvent to about 1/3, which was dissolved in ethyl acetate (80 ml) and washed five times with water (20 ml). After concentrating the organic layer under reduced pressure, acetonitrile (10 ml) was added to the residue, which was again concentrated under reduced pressure, and the resulting crystals were filtered off and dried to obtain the title compound (439.1 mg, yield 91%).

[0106] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 438.14, found (M+H)⁺ = 439.3

Example 8. Preparation of compound No. 272

[0107] In a similar method to working Example 7, the title compound was obtained.

[0108] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 454.14, found (M+H)⁺ = 455.3

Example 9. Preparation of compound No. 65

[0109] 2-nitroaniline (829 mg, 6 mmol) and 1-methylindole carboxaldehyde (1242 mg, 7.8 mmol) were dissolved in 20 ml of tetrahydrofuran, to which acetic acid (200 µl) and NaBH(OAc)₃ (5087 mg, 24 mmol) were sequentially added and stirred at room temperature overnight. A saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with ethyl acetate, dried with anhydrous sodium sulfate, and the solvent was evaporated. After purification by silica gel column chromatography (hexane : ethyl acetate = 95:5), ((1-methylindole-3-yl)methyl)(2-nitrophenyl)amine was obtained (264 mg, yield 18%).

[0110] ((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (264 mg, 0.939 mmol) was dissolved in ethanol (10 ml),

and Pd-C (50 mg, 10% Pd, 0.047 mmol) was added thereto, and stirred in hydrogen atmosphere at room temperature for 6 hours. After the reaction was complete, Pd-C was filtered off and the solvent was evaporated to obtain ((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (212 mg, yield 90%).

[0111] ((1-methylindole-3-yl)methyl)(2-aminophenyl)amine (212 mg, 0.845 mmol) was dissolved in pyridine (1 ml), and carbon bisulfide (1 ml, 16.9 mmol) was added thereto. The mixture was refluxed in nitrogen atmosphere for 1 hour. After the solvent was evaporated, it was purified by silica gel column chromatography (hexane : ethyl acetate = 2:1) to obtain ((1-methylindole-3-yl)methyl)benzimidazole-2-thiol (96 mg, yield 39%).

[0112] Sodium hydride (12 mg, 0.342 mmol) and dimethylformamide (2 ml) were added to a previously dried reaction vessel. To the mixture were added ((1-methylindole-3-yl)methyl)benzimidazole-2-thiol (50 mg, 0.171 mmol) and 2-bromomethyl benzoic acid methyl ester (59 mg, 0.257 mmol), and then the mixture was stirred at 60°C for 1 hour. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2:1) to obtain 2-((1-((1-methylindole-3-yl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (54 mg, yield 74%).

[0113] To 2-((1-((1-methylindole-3-yl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (54 mg, 0.122 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml), 4N aqueous lithium hydroxide solution (0.5 ml) was added. After stirring at room temperature overnight, 6N hydrochloric acid was added to stop the reaction, followed by extraction with ethyl acetate. After washing the ethyl acetate phase with saturated saline, it was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (48 mg, yield 92%).

[0114] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 427.14, found (M+H)⁺ = 428.2

Example 10.

[0115] The compounds in the above Table 47 were synthesized using various halide ester derivatives in a similar manner to Working Example 9. The compounds were confirmed by identification of molecular weight using LC-MS.

Example 11. Preparation of compound No. 51

[0116] Sodium hydride (104 mg, 2.86 mmol) and tetrahydrofuran (16 ml) were added to a previously dried reaction vessel. To the mixture were added 2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester (428 mg, 1.43 mmol) and 2-(bromomethyl)benzoic acid t-butyl ester (466 mg, 3.46 mmol), and then the mixture was stirred at 60°C for 50 minutes. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to obtain 2-((1-((2-((t-butyl)oxycarbonyl)phenyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (495 mg, yield 71%).

[0117] To 2-((1-((2-(t-butyl)oxycarbonyl)phenyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (248 mg, 0.51 mmol) 4N hydrochloric acid in dioxane (1.26 ml, 5.1 mmol) was added, and stirred at room temperature overnight. After the solvent was evaporated, it was dried under reduced pressure to obtain 2-((2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)methyl) benzoic acid (220 mg, yield quantitative).

[0118] 2-((2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)methyl) benzoic acid (180 mg, 0.42 mmol) was dissolved in chloroform (6 ml), to which HOBT (68 mg, 0.504 mmol), aniline (46 µl, 0.504 mmol), t-butanol (1.2 ml) and EDCI (97 mg, 0.504 mmol) were sequentially added and stirred overnight at room temperature. Water was added thereto, followed by extraction with dichloromethane. After drying with anhydrous sodium sulfate, it was filtered, and the solvent was evaporated. It was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((1-((2-(N-phenylcarbamoyl)phenyl)methylthio)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (86 mg, yield 40%).

[0119] To the thus obtained 2-((1-((2-(N-phenylcarbamoyl)phenyl)methylthio)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (86 mg, 0.169 mmol) in tetrahydrofuran (2 ml) and methanol (1 ml), 4N aqueous lithium hydroxide solution (0.5 ml) was added, and stirred at 60°C for about 2 hours. 6N aqueous hydrochloric acid solution was added to stop the reaction, which was extracted with ethyl acetate. After washing the ethyl acetate phase with saturated saline, it was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound (83 mg, yield quantitative).

[0120] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 493.15, found (M+H)⁺ = 494.2

Example 12.

[0121] In a similar method to Working Example 11, the compounds shown in the above Table 48 were obtained using various benzoic acid ester derivatives. The compounds were confirmed by identification of molecular weight using LC-MS.

Example 13. Preparation of compound No. 619

[0122] Sodium hydride (400 mg, 10.0 mmol) and dimethylformamide (30 ml) were added to a previously dried reaction vessel. To the mixture were added 2-(benzimidazole-2-ylthiomethyl)benzoic acid methyl ester (1500 mg, 5.0 mmol) and bromoacetate t-butyl ester (1463 mg, 7.5 mmol), and the mixture was stirred at 80°C for 2 hours. Water was added thereto, followed by extraction with ether. After the ether phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 5:1) to obtain 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)acetic acid t-butyl ester (1298 mg, yield 63%).

[0123] To 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)acetic acid t-butyl ester (1290 mg, 3.13 mmol), trifluoroacetic acid (15 ml) was added, and stirred at room temperature overnight. After the solvent was evaporated, it was dried under reduced pressure to obtain 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)acetic acid (715 mg, yield 64%).

[0124] 2-(2-((2-(methoxycarbonyl)phenyl)methylthio)benzimidazoly)acetic acid (35 mg, 0.1 mmol) was dissolved in tetrahydrofuran (3 ml), to which aniline (11.2 mg, 0.12 mmol) and EDCI (23 mg, 0.12 mmol) were added, and then the mixture was stirred overnight at room temperature. Water was added thereto, followed by extraction with ethyl acetate. After drying with anhydrous sodium sulfate, it was filtered, the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((1-((N-phenylcarbamoyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (27.5 mg, yield 64%).

[0125] 2-((1-((N-phenylcarbamoyl)methyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (20 mg, 0.046 mmol) thus obtained was subjected to hydrolysis as in Working Example 1 to obtain the title compound (6.9 mg, yield 36%).

[0126] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 417.11, found (M+H)⁺ = 418.0

Example 14

[0127] In a similar method to Example 13, the compounds shown in the above Table 49 were obtained using various aniline derivatives.

[0128] The compounds were confirmed by identification of molecular weight using LC-MS.

Table 49

Compound No.	Calculated	M Found (M+H) ⁺	Yield (Overall) %
622	431.13	432.3	5
621	431.13	432.3	5
620	431.13	432.3	21
637	447.13	448.2	13
636	117.13	448.1	23
635	447.13	448.3	44
642	442.11	443.2	27
657	467.13	488.1	19

Table 50

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
765	457.15	458.2	5
767	457.15	458.2	32

10

Table 51

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
866	434.13	435.2	76
869	456.11	457.3	83
904	468.09	469.1	52
937	436.15	437.2	61

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20

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Table 52

Compound No.	Calculated M	Found (M+H) ⁺	Yield (Overall) %
953	476.18	477.2	36
985	428.18	429.2	67
977	400.15	401.4	2

Reference Example 6. Preparation of 2-((1-(2-hydroxyethyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester

35

[0129] To 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl) benzoic acid methyl ester (326 mg, 1 mmol) obtained in Reference Example 2 in dimethylformamide, potassium carbonate (207 mg, 1.5 mmol) and 2-bromoethanol (150 mg, 1.2 mmol) were added, and the resulting solution was stirred at 80°C for 12 hours. After the reaction was complete, it was extracted with ether and the solvent was evaporated. The residue was purified by a flash column chromatography (hexane : ethyl acetate = 4:1) to obtain the title compound (248 mg, yield 67%).

[0130] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 370.14, found (M+H)⁺ = 371.2

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Example 15. Preparation of compound No. 736

[0131] To 2-((1-(2-hydroxyethyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzoic acid methyl ester (45 mg, 0.23 mmol) in N-methylmorpholine (3 ml), PPh₃ (62 mg, 0.24 mmol) and DEAD (10.6 ml, 40% in toluene, 0.24 mmol) were added and the mixture was stirred at room temperature. After 10 minutes, phenol (11.3 mg, 0.12 mmol) was added thereto, which was stirred at room temperature for 12 hours. The solvent was evaporated and the residue was purified by thin layer chromatography (hexane : ethyl acetate = 1:1) to obtain 2-((5,6-dimethyl-1-(2-phenoxyethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (44 mg, yield 81%).

[0132] Using 2-((5,6-dimethyl-1-(2-phenoxyethyl)benzimidazole-2-ylthio)methyl)benzoic acid methyl ester (35 mg, 0.078 mmol) in a similar method to Example 1, a hydrolysis reaction was carried out to obtain the title compound (31 mg, yield 94%). The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 432.15, found (M+H)⁺ = 433.2

Example 16.

[0133] In a similar method to Example 15, the compounds shown in the above Table 50 were obtained using various phenol derivatives.

5 [0134] The compounds were confirmed by identification of molecular weight using LC-MS.

Example 17.

Preparation of compound No. 825

10 [0135] To an ester (33 mg, 0.075 mmol) of compound No. 68 obtained in Example 2 in dichloromethane, 50 to 60% m-chloroperbenzoic acid (26 mg, 0.083 mmol) was added while cooling on ice. After the resulting solution was stirred on ice for 2 hours, a saturated sodium hydrogen carbonate solution was poured and the solution obtained was extracted with chloroform. After washing the chloroform phase with water, it was concentrated and the residue was purified by thin layer chromatography (hexane : ethyl acetate = 1:1) to obtain 2-(((5,6-dimethyl-1-(1-naphthylmethyl)benzimidazole-2-yl)sulfinyl)methyl)benzoic acid methyl ester (7.1 mg, yield 21%).

15 [0136] In a manner similar to Example 1, this was subjected to hydrolysis to obtain the title compound (5.2 mg, yield 76%).

20 [0137] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 440.12, found (M+H)⁺ = 441.3

Example 18. Preparation of compound No. 869

25 [0138] To an ester (39 mg, 0.094 mmol) of compound No. 37 obtained in Example 2 in dichloromethane (5 ml), 50 to 60% m-chloroperbenzoic acid (64 mg, 0.374 mmol) was added while cooling on ice. After the resulting solution was stirred at room temperature for 4 hours, a saturated sodium hydrogen carbonate solution was poured and the solution obtained was extracted with chloroform. After washing the chloroform phase with water, it was concentrated and the residue was purified by flash layer chromatography (hexane : ethyl acetate = 5:1) to obtain 2-(((1-((2,5-dimethylphenyl)methyl)benzimidazole-2-yl)sulfonyl)methyl)benzoic acid methyl ester (37 mg, yield 87%).

30 [0139] In a manner similar to Example 1, 2-(((1-((2,5-dimethylphenyl)methyl)benzimidazole-2-yl)sulfonyl)methyl)benzoic acid methyl ester (64 mg, 0.14 mmol) was subjected to hydrolysis to obtain the title compound (53 mg, yield 87%).

35 [0140] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 434.13, measured (M+H)⁺ = 435.2

Example 19.

40 [0141] In a manner similar to Example 18, the compounds shown in the above Table 51 were synthesized using the esters of the compounds obtained in Working Example 2. The compounds were confirmed by identification of molecular weight using LC-MS.

Example 20. Preparation of compound No. 952

45 [0142] To 5,6-dimethylbenzimidazole-2-thiol (713 mg, 4 mmol) in dimethylformamide (10 ml), triethylamine (836 μ l, 6 mmol) and 2-bromomethylbenzonitrile (1176 mg, 6 mmol) were added. After stirring at 80°C overnight, water was added to the mixture, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:2) to obtain 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (1159 mg, yield 99%).

50 [0143] Sodium hydride (178 mg, 4.90 mmol) and tetrahydrofuran (30 ml) were added to a previously dried reaction vessel. To the mixture were added 2-((5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (719 mg, 2.45 mmol) and 2,5-dichlorobenzyl chloride (543 μ l, 4.90 mmol), and the mixture was stirred at 60°C for 40 minutes. Water was added thereto, followed by extraction with ethyl acetate. After the ethyl acetate phase was dried with anhydrous sodium sulfate, it was concentrated, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to obtain 2-((1-((2,5-dimethylphenyl)methyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (370 mg, yield 37%).

55 [0144] 2-((1-((2,5-dimethylphenyl)methyl)-5,6-dimethylbenzimidazole-2-ylthio)methyl)benzenecarbonitrile (165

mg, 0.401 mmol) was dissolved in toluene (3 ml), to which Me_3SnN_3 (124 mg, 0.602 mmol) was added, and refluxed in nitrogen atmosphere overnight. After the reaction was complete, the solvent was evaporated, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 19:1) to obtain the title compound (75 mg, yield 41%).

- 5 [0145] The compound was confirmed by identification of molecular weight using LC-MS.

Calculated M = 454.19, found $(\text{M}+\text{H})^+$ = 455.2

Example 21.

- 10 [0146] In a manner similar to Example 20, the compounds shown in the above Table 52 were obtained.
 [0147] The compounds were confirmed by identification of molecular weight using LC-MS.

Example 22. Preparation of recombinant human mast cell chymase

- 15 [0148] Recombinant pro-type human mast cell chymase was prepared according to the method reported by Urada et al. (Journal of Biological Chemistry 266: 17173, 1991). Thus, a culture supernatant of the insect cell (Tn5) infected with a recombinant baculovirus containing cDNA encoding human mast cell chymase was purified by heparin Sepharose (Pharmacia). After it was further activated by the method reported by Murakami et al. (Journal of Biological Chemistry 270: 2218, 1995), it was purified with heparin Sepharose to obtain an activated human mast cell chymase.

Example 23. Determination of the activity of inhibiting recombinant human mast cell chymase

- 25 [0149] After a DMSO solution (2 μl) containing the compound of the present invention was added to 50 μl of buffer A (0.5-3.0 M NaCl, 50 mM Tris-HCl, pH 8.0) containing 1.5 ng of the activated human mast cell chymase obtained in working Example 22, 50 μl of buffer A containing, as a substrate, 0.5 mM succinyl-alanyl-histidyl-prolylphenylalanyl-paranitroanilide (Bacchem) was added thereto and the mixture was allowed to react at room temperature for 5 minutes. Changes in absorbance at 405 nm with time were measured to evaluate the inhibitory activity.

- 30 [0150] As a result, IC₅₀ = not smaller than 1 nM and less than 10 nM was observed in compounds No. 63, 64, 65, 143, 174, 256, 264, 272, 311, 354, 319, 349, 358, 395, 401, and 402, and IC₅₀ = not smaller than 10 nM and not greater than 100 nM was observed in compounds No. 37, 50, 84, 115, 117, 119, 121, 123, 130, 147, 168, 256, 320, 321, 324, 352, 355, 364, 380, 392, 398, 444, 455, 459, 460, 506, 863, 866, and 869.

- 35 [0151] As hereinabove described, the benzimidazole derivatives of the present invention exhibit a potent chymase inhibitory activity. Thus, it was revealed that the benzimidazole derivatives of the present invention are clinically applicable inhibitory substances for human chymase activity and can be used for prevention and/or therapy of various diseases in which human chymase is involved.

Example 24. Manufacture of tablets

- 40 [0152] Tablets comprising, per tablet, the following were manufactured:

45	Compound (No. 37)	50 mg
	Lactose	230 mg
	Potato starch	80 mg
	Polyvinylpyrrolidone	11 mg
50	Magnesium stearate	5 mg

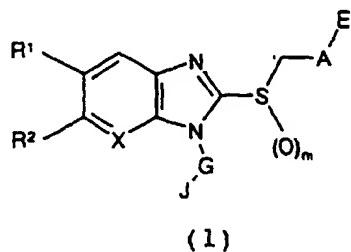
- 55 [0153] The compound of the present invention (the compound in Working Example 2), lactose and potato starch were mixed, and the mixture was evenly soaked in 20% polyvinylpyrrolidone in ethanol. The mixture was filtered through a 20 nm mesh, dried at 45°C, and filtered again through a 15 nm mesh. Granules thus obtained were mixed with magnesium stearate and were compressed into tablets.

Industrial Applicability

[0154] The thiobenzimidazole derivatives of the present invention and the medically acceptable salts thereof exhibit a potent activity of inhibiting human chymase. Thus, said thiobenzimidazole derivatives and the medically acceptable salts thereof can be used, as a human chymase inhibitor, as clinically applicable preventive and/or therapeutic agents for inflammatory diseases, allergic diseases, diseases of respiratory organs, diseases of circulatory organs, or diseases of bone/cartilage metabolism.

Claims

- 10 1. A thiobenzimidazole derivative represented by the following formula (1):



wherein,

- 25 R¹ and R², simultaneously or independently of each other, represent a hydrogen atom, a halogen atom, a trihalomethyl group, a cyano group, a hydroxy group, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R² together form -O-CH₂-O-, -O-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-, in which the carbons may be substituted with one or a plurality of alkyl groups having 1 to 4 carbons;
- 30 A represents a single bond, a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group;
- 35 E represents COOR³, SO₃R³, CONHR³, SO₂NHR³, a tetrazole group, a 5-oxo-1,2,4-oxadiazole group or a 5-oxo-1,2,4-thiadiazole group in which R³ represents a hydrogen atom, or a linear or branched alkyl group having 1 to 6 carbons;
- 40 G represents a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons that may be interrupted with one or a plurality of O, S, SO₂, and NR³, in which R³ is as defined above and the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a trihalomethyl group, a trihalomethoxy group, a phenyl group, or an oxo group;
- 45 m represents an integer of 0 to 2;
- 50 when m is 0 and A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring;
- 55 when m is 0 and A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a sub-

stituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring; or

when m is 0 and A is a single bond or when m is 1 or 2, then J represents a substituted or unsubstituted, linear, cyclic or branched alkyl group having 1 to 6 carbons, a substituted or unsubstituted aryl group having 6 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, in which the substituent represents a halogen atom, OH, NO₂, CN, a linear or branched alkyl group having 1 to 6 carbons, a linear or branched alkoxy group having 1 to 6 carbons (the substituents may be joined to each other at adjacent sites via an acetal bond), a linear or branched alkylthio group having 1 to 6 carbons, a linear or branched alkylsulfonyl group having 1 to 6 carbons, a linear or branched acyl group having 1 to 6 carbons, a linear or branched acylamino group having 1 to 6 carbons, a substituted or unsubstituted anilide group, a trihalomethyl group, a trihalomethoxy group, a phenyl group, an oxo group, a COOR³ group, or a phenoxy group that may be substituted with one or more halogen atoms, and in which the substituents may be independently substituted at any one or more sites of the ring or the alkylene group; and

X represents CH or a nitrogen atom;
or a medically acceptable salt thereof (hereinafter referred to as "the thiobenzimidazole derivative of the present invention").

2. The thiobenzimidazole derivative according to claim 1 characterized in that, in the above formula (1), A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, a substituted or unsubstituted arylene group having 6 to 11 carbons, or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

25 3. The thiobenzimidazole derivative according to claim 1 or 2 characterized in that, in the above formula (1), A is a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

4. The thiobenzimidazole derivative according to any one of claims 1, 2, and 3 characterized in that, in the above formula (1), m is 1, or a medically acceptable salt thereof.

30 5. The thiobenzimidazole derivative according to any one of claims 1, 2, and 3 characterized in that, in the above formula (1), m is 2, or a medically acceptable salt thereof.

35 6. The thiobenzimidazole derivative according to any one of claims 1, 2, and 3 characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted, linear or branched alkylene group having 1 to 6 carbons, and J is a substituted or unsubstituted aryl group having 7 to 9 carbons, a substituted aryl group having 10 to 11 carbons, or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

40 7. The thiobenzimidazole derivative according to any one of claims 1, 2, and 3 characterized in that, in the above formula (1), m is 0, A is a substituted or unsubstituted arylene group having 6 to 11 carbons or a substituted or unsubstituted heteroarylene group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, and J is a substituted or unsubstituted aryl group having 6 to 11 carbons or a substituted or unsubstituted heteroaryl group having 4 to 10 carbons that may contain one or a plurality of oxygen, nitrogen and sulfur atoms on the ring, or a medically acceptable salt thereof.

45 8. The thiobenzimidazole derivative according to any one of claims 1 to 7 characterized in that, in the above formula (1), G is -CH₂-, -CH₂-CH₂-, -CH₂CO-, -CH₂CH₂O-, -CH₂CONH-, -CO-, -SO₂-, -CH₂SO₂-, -CH₂S- or -CH₂CH₂S-, or a medically acceptable salt thereof.

50 9. The thiobenzimidazole derivative according to any one of claims 1 to 8 characterized in that, in the above formula (1), R¹ and R² simultaneously represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons or an alkoxy group having 1 to 4 carbons, or R¹ and R², independently of each other, represent a hydrogen atom, a halogen atom, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, a trihalomethyl group, a cyano group, or a hydroxy group, or a medically acceptable salt thereof.

55 10. The thiobenzimidazole derivative according to any one of claims 1 to 9 characterized in that, in the above formula

(1), E represents COOH or a tetrazole group, or a medically acceptable salt thereof.

11. The thiobenzimidazole derivative according to any one of claims 1 to 10 characterized in that, in the above formula
(1), X represents CH, or a medically acceptable salt thereof.

5 12. The thiobenzimidazole derivative according to any one of claims 1 to 11 characterized by having an activity of inhib-
iting human chymase, or a medically acceptable salt thereof.

10 13. A pharmaceutical composition comprising at least one thiobenzimidazole derivative according to any one of claims
1 to 12 or a medically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 which is a preventive and/or therapeutic agent of a disease.

15 15. A preventive and/or therapeutic agent according to claim 14 wherein said disease is an inflammatory disease, an
allergic disease, a disease of respiratory organs, a disease of circulatory organs, or a disease of bone/cartilage
metabolism.

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INTERNATIONAL SEARCH REPORT		International application No. PCT/JP99/03799																		
A. CLASSIFICATION OF SUBJECT MATTER Int.C1 ⁶ C07D235/28, A61K31/415																				
According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.C1 ⁶ C07D235/28, A61K31/415																				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), REGISTRY (STN)																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category*</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">US, 5124336, A (Laboratoires UPSA), 23 June, 1992 (23. 06. 92) & FR, 2658511, A</td> <td style="padding: 2px;">1, 2, 8-15</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;"></td> <td style="padding: 2px;">3-7</td> </tr> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">J. Med. Chem., 36(9), 1175-87 (1993)</td> <td style="padding: 2px;">1, 2, 8-15</td> </tr> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">JP, 5-155858, A (Laboratories UPSA), 22 June, 1993 (22. 06. 93) & US, 5021443, A & FR, 2658511, A & CA, 2035710, A & EP, 442820, A</td> <td style="padding: 2px;">1, 2, 8-15</td> </tr> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">Chem. Abs. 85, 172661 (1976)</td> <td style="padding: 2px;">1, 2, 8-12</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US, 5124336, A (Laboratoires UPSA), 23 June, 1992 (23. 06. 92) & FR, 2658511, A	1, 2, 8-15	A		3-7	X	J. Med. Chem., 36(9), 1175-87 (1993)	1, 2, 8-15	X	JP, 5-155858, A (Laboratories UPSA), 22 June, 1993 (22. 06. 93) & US, 5021443, A & FR, 2658511, A & CA, 2035710, A & EP, 442820, A	1, 2, 8-15	X	Chem. Abs. 85, 172661 (1976)	1, 2, 8-12
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